422

NCI/ICRDB/SL-422

PB81-929401

NEWARK PUBL'C LIBRARY
MAR 27 1981
U. S. GOVT. PUBS.
DEPOSITORY 376

SPECIAL LISTING

ICRDB
DATA BANK
RESEARCH
COLLECTION
ANALYSIS
DISSEMINATION
APPLICATION

CURRENT CANCER RESEARCH

on

GYNECOLOGIC CANCER: ETIOLOGY, EPIDEMIOLOGY, DIAGNOSIS, AND THERAPY

FEBRUARY 1981

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service ● National Institutes of Health ●
National Cancer Institute

A SERVICE OF THE
INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB)

HE 20. 3173:

Dear Cancer Researcher:

This **SPECIAL LISTING** of Current Cancer Research Projects is a publication of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) Program of the National Cancer Institute. Each **LISTING** contains descriptions of ongoing projects in one selected cancer research area. Approximately 50 different cancer research areas are covered by a separate **SPECIAL LISTING.**

The present series of **SPECIAL LISTINGS** is a third edition, and begins with number 201. This series will update the second edition which included **SPECIAL LISTINGS** numbered 101 through 147. Depending on the total number and types of cancer research summaries received, the third edition will have at least 47 titles, and possibly a few more. In most cases, each third edition **SPECIAL LISTING** will replace the exact subject area of a second edition **LISTING** (SL 201 replacing SL 101, etc.). Whenever the number and variety of summaries requires a change in this procedure, a notation will be made in the specific **LISTINGS** affected.

The purpose of these **LISTINGS** is to promote and facilitate the exchange of information among cancer scientists. The project descriptions in the **LISTINGS** are provided by cancer scientists from more than 50 different countries. Researchers are urged to prepare accurate summaries which will be rapidly processed for inclusion in the CANCERPROJ data base as well as future **SPECIAL LISTINGS.**

These **LISTINGS** are prepared for the ICRDB Program by the Current Cancer Research Project Analysis Center (CCRESPAC) which is operated for the ICRDB Program by the Smithsonian Science Information Exchange (SSIE). Extensive editing of the summaries is not attempted by CCRESPAC, although some minor editorial changes may be required to clarify titles or text. CCRESPAC tries to update each summary on approximately a yearly basis. Unfortunately, due to the volume and the numerous sources of summaries, occasionally some of the summaries may not be updated annually.

IF YOU ARE A PRINCIPAL INVESTIGATOR and find your summary in this **SPECIAL LISTING** to be out of date, inaccurate, or incomplete, please prepare and send a new summary to the CCRESPAC PROJECT OFFICER at the address below as soon as possible. Please also check the address of your project for completeness and accuracy. If the addresses of co-investigators are different from the Principal Investigator's, add their addresses at the bottom of the new project summary. A copy of the Project Registration Form can be found in the back of this **LISTING.**

ICRDB Program Office
National Cancer Institute
Blair Building, Room 114
8300 Colesville Road
Silver Spring, Maryland 20910

Researchers who have summaries (project descriptions) in a given **LISTING** automatically receive complimentary copies of that **LISTING.** Additional copies of this **LISTING** or other **LISTINGS** can be purchased from the National Technical Information Service (see order form in back of this **LISTING**).

Descriptions of more than 20,000 other current cancer-related projects can be retrieved via online computer terminals at more than 800 locations in the U.S. and 12 countries. Any organization linked to the MEDLARS/MEDLINE System at the National Library of Medicine has access to this online file of research project summaries called "CANCERPROJ."

READEX FICHE best copy available

NCI/ICRDB/SL-422
(Updates NCI/ICRDB/SL 322)

RESEARCH AREAS

Abstract Number

I. ETIOLOGY OF GYNECOLOGICAL CANCERS 1
- A. ROLE OF HORMONES IN CARCINOGENESIS OF THE REPRODUCTIVE SYSTEM 1
  - 1. RELATIONSHIP OF EXOGENOUS HORMONES TO HUMAN GYNECOLOGICAL CANCERS 1
  - 2. ENDOGENOUS HORMONES AND GYNECOLOGICAL CANCERS 32
  - 3. HORMONAL INDUCTION OF EXPERIMENTAL GYNECOLOGICAL CANCERS 49
  - 4. HORMONE RECEPTORS AND GYNECOLOGICAL CANCERS 58
- B. ROLE OF VIRUSES IN GYNECOLOGICAL CANCERS 85
  - 1. RELATIONSHIP OF HERPESVIRUSES TO GYNECOLOGICAL CANCERS 85
  - 2. ROLE OF OTHER VIRUSES IN GYNECOLOGICAL CANCERS 114
- C. RADIATION AND CHEMICAL INDUCTION OF EXPERIMENTAL GYNECOLOGICAL CANCERS 120

II. EPIDEMIOLOGY OF GYNECOLOGICAL CANCERS 124
- A. EPIDEMIOLOGICAL STUDIES OF CERVICAL CANCER 124
- B. EPIDEMIOLOGICAL STUDIES OF ENDOMETRIAL CANCER 165
- C. EPIDEMIOLOGICAL STUDIES OF OVARIAN CANCER 172
- D. EPIDEMIOLOGICAL STUDIES OF MULTIPLE GYNECOLOGICAL CANCERS 185
- E. GYNECOLOGICAL CANCER REGISTRIES 193

III. STUDIES OF TROPHOBLASTIC NEOPLASMS 206

IV. TERATOCARCINOMAS 219
- A. BIOCHEMICAL CHARACTERISTICS OF TERATOCARCINOMAS 219
- B. DIFFERENTIATION OF TERATOCARCINOMAS 226
- C. GENETIC STUDIES OF TERATOCARCINOMAS 245

V. BIOCHEMISTRY, IMMUNOLOGY, HISTOPATHOLOGY AND CYTOLOGY OF GYNECOLOGICAL CANCERS 264
- A. BIOCHEMICAL STUDIES OF GYNECOLOGICAL CANCERS 264
- B. IMMUNOLOGY OF GYNECOLOGICAL CANCERS 278
- C. HISTOPATHOLOGY AND CYTOLOGY OF GYNECOLOGICAL CANCERS 291

VI. SCREENING, DIAGNOSIS, AND PROGNOSIS OF GYNECOLOGICAL CANCERS 321
- A. CERVICAL AND OTHER GYNECOLOGICAL SCREENING PROGRAMS 321
- B. STUDIES ON THE DEVELOPMENT OF AUTOMATED CYTOLOGY SCREENING METHODS 340
- C. IMMUNODIAGNOSTIC AND PROGNOSTIC STUDIES 347
- D. OTHER DIAGNOSTIC AND PROGNOSTIC STUDIES 361

VII. THERAPY OF GYNECOLOGICAL CANCERS 382
- A. THERAPY OF CERVICAL CARCINOMA 382
- B. THERAPY OF OVARIAN CARCINOMA 400
- C. THERAPY OF UTERINE CANCER 427
- D. THERAPY OF MULTIPLE GYNECOLOGICAL CANCERS 438
- E. MEMBERS OF GYNECOLOGIC ONCOLOGY GROUP 447

Investigator Index

NOTE: If you are a Principal Investigator with a research project registered with the ICRDB, you are entitled to two complimentary subscriptions of CANCERGRAMS. If you are NOT receiving CANCERGRAMS, be sure to mention this in your next correspondence with the Program.

CURRENT CANCER RESEARCH

I. ETIOLOGY OF GYNECOLOGICAL CANCERS

A. ROLE OF HORMONES IN CARCINOGENESIS OF THE REPRODUCTIVE SYSTEM

1. RELATIONSHIP OF EXOGENOUS HORMONES TO HUMAN GYNECOLOGICAL CANCERS

1. HORMONAL CONTRACEPTION AS A FACTOR IN GYNECOLOGICAL CANCER

Radzuweit, H., Frauenklinik Bezirkskrankenhauses Cottbus, *Thiemstrasse 111, 75 Cottbus, German Democratic Republic*

Prolonged intake of hormonal contraceptives as a possible cause of increased risk for a gynecological cancer has been discussed many times. Several studies contradict this relationship. Using data from patients with colon, corpus uteri and ovarian carcinoma, this problem is again being analyzed for the period 1978-85. All female patients with carcinomas of these sites are being questioned about the period and the time they have taken contraceptives. Using controls, the frequency of intake of hormonal contraceptives in the total female population of this region will be deduced.

2. INFLUENCE OF HORMONAL CONTRACEPTION ON CERVICAL LESIONS

Torres, A. F., Pala, F. L., Hospital General de St. Antonio, Serv Ginecologia e Patologia, *Porto, Portugal*

Cervix dysplasia frequency will be studied in a hundred high risk patients aged 30-40 who have used the same oral contraceptive (Ethynyl-Estradiol 0.05 mg and D-Norgestrel 0.25 mg) during a whole year. The control group will be one hundred women of the same age with the same risk factors. Cervical smear, colposcopy and guided biopsy will be used.

3. CASE-CONTROL STUDY OF THE POSSIBLE RELATIONSHIP BETWEEN ORAL CONTRACEPTIVES AND CANCERS OF THE BREAST, ENDOMETRIUM AND OVARY

Vessey, M. P., Doll, R. R., McPherson, K., University of Oxford, Dept. of Social & Community Medicine, *S. Parks Rd., Oxford OX2 6HE, England, United Kingdom*

Although a great deal is known about the short- and medium-term hazards of oral contraceptives, there is still a great need to monitor possible carcinogenic effects. In this investigation, women of childbearing age newly presenting with cancers of the reproductive system at any of six London teaching hospitals are interviewed, together with matched controls. The study has been in progress for about eight years and now includes nearly 1,000 cases of cancer of the breast. Results concerning the first 90 cases of breast cancer were published in the British Medical Journal in September 1972, the next 232 cases in the Lancet in April 1975, and the next 385 cases in the British Medical Journal in July 1979.

4. CASE-CONTROL STUDY OF NEOPLASIA AND STEROID CONTRACEPTIVES

Molina, R., Dabancens, A., Martinez, L., Salas, C. O., Universidad de Chile, Jose Joaquin Aguirre Clinical Hospital, Obstetricia y Ginecologia, *1058 Av. Bernardo O'Higgins, Santiago, Chile*

OBJECTIVE: To assess the carcinogenic risks of steroidal contraceptives.

APPROACH: A case-control study will be in progress for the next five years including every new patient with histologically confirmed cervical, endometrial and ovarian carcinoma. Two controls of the same age, socioeconomic level and origin will be chosen to answer the same questionnaire on contraceptive history as the women with carcinoma.

5. COLLABORATIVE STUDY OF NEOPLASIA AND STEROID CONTRACEPTIVES

Modan, B., Ron, E., Thomas, D. B., Gray, R., Chaim Sheba Medical Center, Dept. of Clinical Epidemiology, *Bitan 27, Tel Hashomer, Ramat Gan, Israel*

This is a collaborative case-control study of malignant neoplasms of the breast, corpus uteri, gallbladder, liver and ovary in relation to oral contraceptives. Approximately 200 cases and double the number of controls are expected to enter the study each year. All study subjects will be interviewed in hospital. The interview schedule contains questions on prior use of oral contraceptives and other methods of contraception, medical history with an emphasis on gynecological and obstetrical history and family medical history. Pathology slides from all cases will be obtained and reviewed by a reference pathologist. This study is also being conducted in Chile, the Philippines, Mexico, Nigeria, Thailand and Australia.

6. ASSOCIATION OF STEROID CONTRACEPTIVE USE AND CERVICAL CARCINOGENESIS

Isarangkul Na Ayuthya, W., Srisupundit, S., Sebastien, P., Mahidol University, School of Medicine, Dept. of Pathology, *Bangkok*, 7, Thailand

The aim is to determine if there is a true association between steroid contraceptive use and cervical carcinogenesis and to identify high-risk groups for whom the use of steroid contraceptives might lead to a significantly increased risk of cervical dysplasia and cancer. A case-control study on women with cervical intraepithelial neoplasia and/or invasive carcinoma in which patients undergoing hysterectomy without histological evidence of the studied diseases serve as controls is being carried out. The two groups will be matched for age, age at first marriage, age at first pregnancy and socio-economic status. The subjects are interviewed for information on matching factors and contraception using a specially designed protocol. Histological sections of both case and control subjects are reviewed and the diagnoses confirmed. Additional serial sections of the cervix are obtained whenever necessary. Three hundred control and 300 case subjects will be investigated. Association will be evaluated by means of relative risks, statistical significance, and confidence interval.

7. CANCER AND STEROID HORMONES

Ory, H. W., U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, *1600 Clifton Rd. N.E., Atlanta, Georgia*, 30333, United States of America

This pilot study represents the field testing stage of an anticipated multicenter national study which will investigate the relationships between oral contraceptives and other hypothesized etiologic factors in the causation of breast, endometrial, and ovarian carcinomas. The pilot phase will consist of population-based identification of cases and random digit dialing selection of controls and collection of data from both groups. This portion of the study will be conducted at five centers throughout the United States.

8. PROGNOSIS OF ENDOMETRIAL CANCER IN RELATION TO ESTROGEN EXPOSURE

Elwood, J. M., Boyes, D. A., Cancer Control Agency of British Columbia, Division of Epidemiology, *2656 Heather St., Vancouver, British Columbia*, V5Z 3J3, Canada

Since 1968, all patients diagnosed as suffering from endometrial cancer seen at the major treatment center in British

Columbia have had information on estrogen and oral contraceptive use recorded by special letters to family doctors. Information on approximately 400 patients diagnosed between 1968 and 1972 has been abstracted, and is being analyzed to assess the relationship between estrogen exposure and type and depth of tumor, and subsequent survival.

9. NATURAL HISTORY OF DYSPLASIA OF THE UTERINE CERVIX

Miller, A. B., Thompson, D. W., Jain, M., National Cancer Inst. of Canada, Epidemiology Unit, Dept. of Preventive Medicine & Biostatistics, *c/o University of Toronto, Toronto, Ontario,* M5S 1A8, Canada

OBJECTIVE: To investigate the natural history of cytologically identified but untreated dysplasia of the uterine cervix and to explore the possible association of oral contraceptive use and the risk of progression of dysplasia.

APPROACH: It is proposed to compare approximately 20,000 cases (minimal, mild, moderate and severe) of dysplasia, identified through the cytopathology records of a private laboratory covering the period from 1962 to 1979, with a control group of women. The controls will be selected as a 2% random sample of approximately 1.5 million records from the same laboratory. Prior to 1975 a substantial number of cases had been observed here without any therapeutic intervention. Care will be taken to avoid duplication of records and to ensure information on all follow-up records. Information is being extracted on name, OHIP or other insurance number, date of birth, date of smear, name of physician, hormone use, oral contraceptive use, residence, clinical diagnosis, treatment, smear interpretation and diagnosis.

The case and control series will be compared for the distribution of identified features by age. Probability of progression or otherwise will be determined by the life-table method. The major comparison will be between the two groups identified, with the endpoint determined in a hierarchical fashion with the most 'severe' being determined. Lists in descending order of severity would be death from cancer of the cervix, diagnosis of clinical invasive cancer of the cervix, diagnosis of occult invasive cancer of the cervix, diagnosis of carcinoma in situ and diagnosis of dysplasia, severe, moderate, mild and minimal.

PROGRESS: Data extraction starting with the year 1962 has been in progress since April 1978.

10. CASE-CONTROL STUDY - RELATION BETWEEN CANCER OF THE ENDOMETRIUM AND ESTROGEN INTAKE

Kewitz, H. P., Jesdinsky, H. J., Freie Universitat Berlin, Inst. fuer Klinische Pharmakologie, *Hindenburgdamm 30, 1000 Berlin 45, Federal Republic of Germany*

Previous epidemiological retrospective studies have shown that there is some evidence of a positive correlation between estrogen intake and endometrial cancer. Patients with endometrial cancer are interviewed, their habits of drug intake determined and compared with two control groups.

11. THE CARCINOGENIC POTENTIAL OF CERTAIN ORAL CONTRACEPTIVE STEROIDS IN FEMALE MONKEYS

Wazeter, F. X., Geil, R. G., International Research & Development Corp., *900 N. Main St., Mattawan, Michigan,* 49071, United States of America

The objective has been to study over a 10-year period, in female Macaca mulatta monkeys, the long-term effects of certain steroids used or proposed for use in oral contraceptives versus placebo. These studies were intended as 'positive controls' for similar studies by industry using their own products. Dosage was oral, in fruit puree, at 2X, 10X, and 50X proposed human dose (mg/kg), versus placebo, in cyclic fashion, 21 days on drug, 7 days off, with at least 16 monkeys per group. Compounds were: progestogens, i.e., ethynerone, chloroethynyl norgestrel (SW-4355), or anagestone acetate in combination with an estrogen, mestranol; and mestranol and ethynerone alone. Of these, only mestranol is present in any marketed oral contraceptive. Parameters studied were: body weights, behavior and survival, vaginal cytology and bleeding, hematology and clotting studies, blood chemistry, including blood glucose, ophthalmologic examinations, and palpable nodules in the mammary area. Metabolic studies of estradiol and of mestranol, using a radioactive label, were conducted by scientists from NCTR in a few monkeys terminally. Histopathology is being done by the contractor on all abnormal tissues and on 27 normal tissues. Some confirmatory histopathology is being done by the Armed Forces Institute of Pathology (AFIP). All monkeys have been necropsied, and final report is due November 30, 1979.

12. EFFECT OF ORAL CONTRACEPTIVES ON CARCINOGEN METABOLISM

Gingell, R., University of Nebraska, Lincoln Campus, Graduate School, *Lincoln, Nebraska,* 68508, United States of America

There has recently been much concern over the possible association of hormone imbalance with human cancer in various organs. Prominent among these are the proposed association between oral contraceptives and the occurrence of benign hepatomas, and the increased incidence of breast and endometrial cancer in post-menopausal women which is accentuated by estrogen therapy. Despite a reported association of oral contraceptives with breast cancer in women and dogs, a positive correlation remains uncertain, and most current epidemiological evidence would suggest a protective role, if any.

13. CANCER RISK AMONG WOMEN EXPOSED TO DES IN PREGNANCY

Colton, T., Adam, E., Kaufman, R. H., Barnes, A. B., Robboy, S. J., Kurland, L., Townsend, D., Dartmouth College, Dartmouth Medical School, Dept. of Community Medicine, *P.O. Box 833, Hanover, New Hampshire,* 03755, United States of America

We propose to conduct an historical cohort study to determine the risks of breast and gynecologic cancers associated with exposure to diethylstilbestrol (DES) during pregnancy. This is a collaborative investigation to be conducted at four study centers and with a central data coordinating center. Study collaborators are participants in the DESAD Project which is an ongoing observational study of women exposed in utero to DES. We anticipate a total cohort of 3,000 mothers exposed during pregnancy, mainly in the early 1950's, whose exposure has been ascertained in the DESAD Project by review of obstetric records. In addition, we shall obtain a control cohort of 3,000 unexposed mothers matched to the exposed by age and date of pregnancy. Exposed and control mothers will be contacted by mail and telephone to provide information on health history, hormone usage and other known risk factors for the cancers of concern. For all suspected cancers of interest, clinical details and pathology slides will be sought from medical sources and reviewed centrally according to a uniform protocol. We calculate that with a cohort of 3,000 each of exposed and unexposed mothers we shall have reasonable power (1 - beta equals .90) of detecting a population relative risk of 1.5 for breast cancer and 1.6 for gynecologic cancers.

14. EXOGENOUS MATERNAL HORMONES AND CANCER IN DAUGHTERS

Herbst, A. L., DeLee, J. B., Johnston, G. A., Scully, R. E., Young, R. H., Robboy, S. J., Taft, P. D., University of Chicago, Pritzker School of Medicine, Dept. of Obstetrics & Gynecology, *5801 S. Ellis Ave., Chicago, Illinois,* 60637, United States of America

The Registry for Research on Hormonal Transplacental Carcinogenesis continues its investigation of the epidemiology, pathogenesis, biologic characteristics, management and prognosis of human genital cancers that develop after intrauterine exposure to exogenous sex hormones. A computerized data bank that contains carefully monitored and doubly checked details for each case forms the basis for this research. We shall continue active canvassing of treatment centers and tumor registries in order to obtain all cases of clear cell adenocarcinoma of the genital tract occurring in females born after 1940, with or without a history of hormone exposure, as well as all cases of other types of genital cancer that develop in individuals exposed to either diethylstilbestrol (DES) or any other type of sex hormones, including those of steroidal nature. Detailed clinicopathologic correlative studies will be directed toward a wide variety of host and cancer characteristics that may be related to the behavior of the tumor (i.e., histology, depth of invasion, mitoses, grade and location). Of particular interest are squamous cell carcinomas of the vagina and cervix that arise in the exposed. The investigation of lesions that precede clear cell adenocarcinoma will continue. Knowledge of treatment and prognosis of these lesions will be expanded. We shall remain a source of scientific information and consultation for this problem.

BIBLIOGRAPHIC REFERENCES: Herbst, A.L., Norusis, M.J., Rosenow, P.J., Welch, W.R., and Scully, R.E.: An analysis of 346 cases of clear cell adenocarcinoma of the vagina and cervix with emphasis on recurrence and survival. Gynecol. Onc. 7:111-122, 1979. Herbst, A.L., Scully, R.E., and Robboy, S.J.: Prenatal DES exposure and human genital tract abnormalities, in Proceedings of the Conference on Perinatal Carcinogenesis. Natl. Cancer Institute Monograph 51:25-35, 1979.

15. STUDY OF GENITAL TRACT ANOMALIES

Townsend, D. E., University of Southern California, School of Medicine, Dept. of Obstetrics & Gynecology, *2025 Zonal Ave., Los Angeles, California*, 90033, United States of America

OBJECTIVES: Identify and study offspring of women who received synthetic estrogens during pregnancy between 1943 and 1963. Repeat examinations at regular intervals, perform diagnosis and follow-up and treatment as necessary. Approximately 1,000 offspring are to be examined on this contract.

PROPOSED COURSE: The contractor will establish standard definition of eligibles and develop suitable approaches to elicit eligibles through information campaigns directed at physicians and general public via mass media. Evaluation will be performed and reported.

PROGRESS: A total of 585 participants had been entered by March 1976. Of these, 508 are active participants, with 374 having documentation of DES exposure in utero. Prenatal record review process has been used to obtain participants. Consent forms have been utilized.

16. EXOGENOUS ESTROGENS AND THE DEVELOPMENT OF CANCER OF BREAST AND ENDOMETRIUM

Morgan, R. W., Vakil, D. V., University of Toronto, Faculty of Medicine, Dept. of Preventive Medicine & Biostatistics, *92 College St., Toronto, Ontario*, M5S 1A8, Canada

This retrospective cohort study is designed to examine the risk of breast cancer and endometrial cancer in menopausal and postmenopausal women who had received estrogen therapy for other than contraceptive purposes. The study group is composed of 1,678 women (ages 40-55) in Toronto, who, between 1960 and 1970, were started on long-term estrogen therapy for menopause (Cohort A). Drug use information and epidemiological data are being obtained from the following sources: gynecologists' records, Ontario Cancer Registry, Ontario Cancer Foundation, and telephone interviews. The incidence rates for breast cancer and endometrial cancer will be compared with age-specific incidence and mortality rates of the female population of Ontario (Cohort B). The mortality rates for the study population will also be compared with age-specific cancer mortality rates of the Canadian female population (Cohort C). An estimate will be made of the relative and attributable risk of developing malignant breast disease or endometrial carcinoma and of dose-response relationships of oestrogens to disease.

17. GYNECOLOGICAL CANCER IN WESTERN AUSTRALIA WITH SPECIAL REFERENCE TO ROLE OF EXOGENOUS AND ENDOGENOUS ESTROGENS IN ENDOMETRIAL CANCER

Armstrong, B. K., Hahnel, R., University of Western Australia, Dept. of Medicine, *Nedlands, W. Australia 6009, Australia*

The study will describe trends in mortality from gynecological cancer in Western Australia between 1930 and 1974 and incidence data collected by cancer registration between 1971 and 1974. The latter data will permit study by area of residence, occupation, race and country of birth. A retrospective case-control study of the role of estrogen therapy with mainly ethinyl estradiol in the etiology of endometrial cancer is being undertaken and will include about 200 cases and 200 controls. Data on estrogen receptors, and plasma and urinary estrogen have been collected already on over 50 patients with endometrial cancer. Data will be collected also for appropriately matched controls and related to physical characteristics, obesity, diet and other factors.

18. POSTMENOPAUSAL ESTROGEN TREATMENT AND ENDOMETRIAL CANCER

Persson, I. R., Johansson, E., Lindberg, B., Smedby, B., Westerholm, B., Manell, P., Uppsala Universitet, Dept. of Obstetrics & Gynecology, *Box 256, S75105 Uppsala, Sweden*

It has been hypothesized that estrogens are related to development of postmenopausal endometrial cancer. Numerous American case-control studies have shown a substantial increase of risk in connection with estrogen replacement therapy. The present study is a prospective one which will follow a sample of some 30,000 estrogen-treated postmenopausal women during an observation period of at least five years to ascertain the incidence of endometrial cancer. The observed incidence in this cohort will be compared to the expected one which will be computed from available cancer statistics. There will be additional studies in this cohort regarding the incidence of mammary cancer and also deep vein thrombosis and gallbladder disease. The large cohort is established by collecting all estrogen prescription forms from a defined geographical region in the center of Sweden. From these prescription forms the identity-number (a ten-digit number) will be collected and stored with the help of computer facilities. All new cases of endometrial cancer will be collected from different pathology departments which serve the same geographical region. All hysterectomized women in the cohort will be excluded by referring to a special computer-based admission diagnoses register. All cases of endometrial cancer will be examined and interviewed to study the distribution of known risk factors. This will be done in samples of the total estrogen cohort and samples from a non-treated healthy population.

19. ESTROGENS AND GENITAL CANCERS - A CASE-CONTROL STUDY

Kelsey, J. L., Fischer, D. B., White, C., LiVolsi, V. A., Holford, T. R., Mostow, E., Goldenberg, I. S., Schwartz, P. E., Morris, J. M., Yale University, School of Medicine, Dept. of Epidemiology & Public Health, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

This is a case-control epidemiological study designed to ascertain whether there are any associations, either positive or negative, between use of exogenous estrogenic hormones for therapy during or following menopause or for oral contraception during reproductive years, and cancer of the corpus uteri, cancer of the breast, and cancer of the ovary. Previous estrogen use in women in the age group 45 to 74 years admitted to several large Connecticut hospitals with a first diagnosis of any of these cancers will be compared to estrogen use in women of the same age group admitted to surgical services in the same hospitals for other conditions. Information on estrogen use and other relevant variables is obtained by means of a standardized structured questionnaire administered by trained interviewers; this is supplemented by information provided by the patient's physician when necessary. Diagnosis of the cancers is confirmed by a pathologist, and particular attention is focused on specific histologic types. The study is now in its second year of data collection. To date, 236 cases of breast cancer, 127 cases of endometrial cancer, 54 cases of ovarian cancer, and 1121 controls have been interviewed and the information keypunched and checked for errors. It is expected that data collection will be complete for breast cancer and endometrial cancer by June, 1979.

20. ENDOMETRIAL CARCINOMA AND ESTROGEN THERAPY

Lauritzen, C., Wolf, A., Universitat Ulm, Frauenklinik, Dept. of Obstetrics & Gynecology, *Prittwitzstr. 43, D7900 Ulm, Federal Republic of Germany*

The results of our retrospective study of possible correlations between a long-term estrogen therapy and endometrial carcinoma have been completed. No correlation has been found between estrogen therapy and endometrial cancer risk in our material paper, published in Brush, King and Taylor: 'Endometrial Cancer,' Bailliere Tindall 1978, pp. 40-46. The research continues.

OBJECTIVES: Evaluation of possible correlations between a long-term estrogen therapy and endometrial carcinoma: An evaluation is done of all patients treated in our clinic with estrogens for complaints during the years 1968 to 1978 with respect to relative risks for thromboembolia myocardial infarction, cervico-vascular insults, liver-gallbladder diseases, hyperlipidemia, diabetes and all types of cancers. These patients will be evaluated especially for their familiar and personal risk factors.

PROGRESS: Our prospective study (follow-up of patients undergoing estrogen therapy) is continuing. Two hundred and forty patients have now been followed for 3 1/2 years during therapy with estriol preparations. First report of the results will be given 1 1/2 years from now when a 5-year prospective study is completed.

21. LONG-TERM CONJUGATED ESTROGEN CYCLIC THERAPY - EFFECTS IN BREAST AND UTERINE PATHOLOGY

Fuensalida, S., Zanartu, J., Dabancens, A., Gonzalez, O., Universidad de Chile, Jose Joaquin Aguirre Clinical Hospital, Gynecology Unit, *1058 Av. Bernardo O'Higgins, Santiago, Chile*

OBJECTIVE: To study the possible carcinogenic effects of prolonged cyclic therapy with (1) conjugated estrogens, and (2) conjugated estrogens in combination with progestogen.

APPROACH: To conduct a prospective study with clinical and histological controls. This study was begun in 1976 and is still under way.

22. LONG-TERM SURVEILLANCE OF MORTALITY AND CANCER INCIDENCE IN WOMEN RECEIVING HORMONE REPLACEMENT THERAPY (HRT)

Adam, S. A., Vessey, M. P., University of Oxford, Dept. of Social & Community Medicine, *S. Parks Rd., Oxford OX2 6HE, England, United Kingdom*

In the proposed investigation women seen at 20 menopause clinics in different parts of the country who (1) are currently using HRT and have been using it continuously for at least one year, or (2) are no longer using HRT, but used it in the past for six months or less, will be recruited and followed up indefinitely using the facilities of the National Health Service Registries. Mortality rates and cancer incidence rates of the short-term and long-term users of HRT will be computed from time to time and comparisons will be made with national mortality and cancer incidence data. Cancer of the endometrium and cancer of the breast are sites of particular interest, as well as cardiovascular disease. It is hoped to recruit around 10,000 women over the next three years for the study. So far 1,544 'long-term' users and 234 'short-term' users have been recruited.

23. SEX STEROIDS AND ENDOMETRIAL NEOPLASIA

LoBue, C., Briggs, R. M., Prince, E., U.S. Dept. of Health & Human Services, Public Health Service, Hospital, *1131 14th Ave. S., Box 1131, Seattle, Washington*, 98114, United States of America

A recent retrospective survey and a few prospective studies have suggested a possible causal relationship between estrogen replacement therapy in menopausal patients and the development of endometrial neoplasia. Studies have further suggested that the addition of cyclical progestin therapy, especially taken for over 10 days, may protect subject women from neoplastic changes or reverse neoplastic changes in subject women. However, few studies sampled the endometrium of subjects before the onset of therapy.

The present proposal would survey endometrial histology in various groups of menopausal women. A prospective study of the effects of estrogen versus placebo on the endometria of subject women will also be undertaken.

24. EDUCATIONAL APPROACHES TO ENDOMETRIAL CANCER CONTROL

Standfast, S. J., Greenwald, P., Janerich, D. T., Lawrence, C. E., Graham, S., Murphy, P., Hoff, M., Doolittle, S., Aliferis, D., State Bureau of Cancer Control, *Empire State Plaza, Tower Bldg. Rm. 565, Albany, New York*, 12237, United States of America

The incidence of endometrial cancer has been rising dramatically in New York State and elsewhere, over the last five years. A strong association between endometrial cancer and estrogen replacement therapy, with a four- to eightfold relative risk has been demonstrated in seven case-control studies. Furthermore, 24% of the women in New York State ages 40-69 have used these drugs according to our recently completed survey. Thus, a continued increase in the incidence of this disease is expected. Although questions remain about the severity of the endometrial cancer epidemic in terms of its effect on mortality, it is only prudent to reduce the level of menopausal estrogen use in light of recent evidence. An education campaign is needed to promote a careful reconsideration of the risks and benefits in each case where these drugs are currently used. Women who have already been exposed should be appraised of their high-risk status and informed about the symptoms and diagnosis of endometrial cancer. In addition, further research to monitor this disease and to find answers to remaining epidemiologic questions must not be neglected. Given the substantial evidence of estrogen exposure as an etiologic factor in this outbreak of endometrial cancer, cancer control through reduced exposure appears to be highly promising. Also, there is evidence that endocervical sampling with Pap tests would improve detection rates for endometrial cancer. Likewise, keener public awareness of symptoms may contribute to early diagnosis. This circumstance may provide an unprecedented opportunity for cancer control, if we can understand from a sociological standpoint the process of motivating women and their physicians to modify their drug use habits and to adopt early detection practices. A program of test demonstrations in public and professional education is planned to determine the most effective means for increasing knowledge and motivating changes in practice. Specific activities planned include: (1) The production of multimedia public education campaign, (2) The formation of a uterine cancer professional education task force and the development of a professional-patient education program in collaboration with medical and nursing schools and professional societies. (Text Abridged.)

25. CANCER IN WOMEN RECEIVING EXOGENOUS ESTROGENS

Arnold, M. F., University of Denver, Denver Research Inst., *University Park, Denver, Colorado*, 80210, United States of America

The issue of replacement estrogen for post-menopausal women has created a variety of controversies in terms of potential benefits and potential risks. This project is concerned primarily with the prevention of estrogen-dependent neoplasia (breast or endometrium). In view of the extensive literature on both the potentially beneficial effects of estrogen treatment and the potentially detrimental effects, there is likely to be disagreement in the professional community and confusion and concern among the patient population and the public.

The plan for the project is to enlist the cooperation of a selected group of physicians to participate in the demonstration by: (a) Following recommended policies for surveillance, diagnosis and treatment, and follow-up for patients for whom they are prescribing estrogenic hormone therapy; and (b) providing data, or access to data collections, regarding therapeutic regimes for their patients on hormones and special information on those patients showing symptoms or signs such as bleeding or mammary masses. Recommended policies for surveillance, diagnosis and treatment, and follow-up of patients will be developed by a Medical Steering Committee sponsored jointly by the Denver Medical Society, the Colorado Division of the American Cancer Society and the CRCC. Participating physicians will be provided consultation on surveillance, diagnosis and treatment of both endometrial and breast cancer as well as consultation for patient education.

A supporting and reinforcing community education program will be directed at women over forty-five.

26. RISKS AND BENEFITS OF THE DECLINE IN ESTROGEN USE BY POSTMENOPAUSAL WOMEN

Palesch, Y. Y., Brody, J. A., White, A., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Inst. on Aging, Epidemiology Demography & Biometry Program, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

OBJECTIVES/ISSUES ADDRESSED: Review the trends in estrogen use in the past decade by peri- and postmenopausal women. Discuss the current status of risks and benefits of estrogen use.

APPROACH/METHODOLOGY: Abstract data on estrogen drug appearance from National Disease and Therapeutic Index volumes (1970-1978). Mortality and incidence data of endometrial cancer for the U.S. is also collected. Review current literature on estrogen as risk or beneficial factor.

MAJOR FINDINGS: A drastic decline in estrogen drug appearance is observed during 1975-76 following the publication of several case-control studies linking estrogen use with endometrial cancer.

27. STUDY OF GENITAL TRACT ANOMALIES

Decker, D. G., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

The Contractor shall: Identify a population of approximately 1000 offspring (males and females) whose mothers received a synthetic estrogen during pregnancy; examine each individual in the population for the purpose of detecting congenital abnormalities or the presence of cancer; develop suitable treatment protocols for each particular diagnosis; and conduct a continuing data analysis, evaluation and assessment of this effort.

28. ENDOMETRIAL CANCER EPIDEMIOLOGY AND CONTROL

Greenwald, P., Lawrence, C. E., Caputo, T., Richart, R., State Bureau of Cancer Control, *Empire State Plaza, Tower Bldg. Rm. 565, Albany, New York*, 12237, United States of America

This epidemiologic study of endometrial cancer monitors the incidence, severity, and mortality trends in a sample of cases reported to the New York State Cancer Registry during the years 1971 through 1981. Cases will be validated through histologic re-examination and re-staging of this sample. This will indicate if incidence is increasing for both advanced and early stages of the disease, and what effect this may have on future mortality rates.

The epidemiologic case-control component of the research focuses on the association between endometrial cancer and the use of estrogens. Specifically, we wish to determine if estrogen use is associated with advanced stage disease, and if there is a risk decline following termination of use. Additionally, we will ascertain through multivariate methods the factors which discriminate low grade and/or early stage cases from high grade, advanced stage cases. One hundred and fifty advanced stage and 200 early stage newly diagnosed endometrial cancer patients will be interviewed. A case to control ratio of 1:2 for advanced stage cases and 1:1 for early stage cases will be used.

29. THE ROLE OF EXOGENOUS ESTROGEN IN NEOPLASIA AND HYPERPLASIA OF THE ENDOMETRIUM

Woolever, C. A., Osborn, R. W. Clarke, E. A., Spengler, R. F., McMaster University, School of Medicine, Dept. of Obstetrics & Gynecology, *1200 Main St. W., Hamilton, Ontario*, L8S 4J9, Canada

The objective is to assess the significance of exogenous estrogen use in the development of endometrial carcinoma and hyperplasia. Newly diagnosed endometrial carcinomas and hyperplasias were obtained from 21 metropolitan hospitals in Toronto. From April 1, 1977 to March 31, 1978, 144 carcinomas and 575 hyperplasias were diagnosed among metropolitan residents. Tissue slides for both case groups were reviewed independently by two senior pathologists. For each of the confirmed carcinoma and hyperplasia cases, two age-matched neighborhood controls were used. Both cases and controls were interviewed in their homes. Detailed information was sought on medications, gynecological histories, episodes of bleeding and associated surgical procedures. The degree of medical surveillance is being assessed in addition to other confounding variables. Interview information is being verified against available medical records from hospitals and physicians' offices. The analysis is expected to be completed by June 1980.

30. CASE-CONTROL STUDY OF THE RELATIONSHIP BETWEEN FEMALE HORMONE USE AND CANCER OF THE BREAST AND ENDOMETRIUM

Slone, D., Shapiro, S., Boston University, School of Medicine, Dept. of Medicine, *80 E. Concord St., Boston, Massachusetts*, 02215, United States of America

An epidemiological study of the case-control type will take place in the context of a large, ongoing study with the following objectives: (1) To design, test and implement an ongoing system of data collection as a resource for generating and testing hypotheses concerning effects of drugs used for long periods of time; (2) to monitor this data to identify previously unrecognized effects of such drugs; (3) to carry out ad hoc analyses of the data to evaluate hypotheses (both those arising from monitoring and from elsewhere); (4) to undertake ad hoc studies outside the monitoring system to provide for further evaluation of certain hypotheses; (5) to provide estimates of when drugs used for long periods appear to be safe. The hypotheses to be evaluated in this study are that female hormones are related to an increased risk of breast and endometrial cancer. The study will be based in hospitals throughout the U.S.A. Specially trained nurses will administer questionnaires to cases and controls to determine descriptive characteristics, prior female hormone and other drug exposure, and presence of known risk factors for cancer of the breast and endometrium. Between 400 and 500 women, each with breast cancer and endometrial cancer, and about ten times that number of controls will be interviewed.

31. MEDICAL, INDUSTRIAL HYGIENE, AND REPRODUCTIVE STUDIES OF WORKERS EXPOSED TO ESTROGENS

Tanaka, S., Zaebst, D., Haring, M., U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, National Inst. for Occupational Safety & Health, Division of Surveillance, Hazard Evaluations & Field Studies, *4676 Columbia Pkwy., Cincinnati, Ohio*, 45226, United States of America

Estrogens are a group of synthetic and natural hormones having serious potential effects on exposed workers. NIOSH hazard evaluation studies which were carried out in chemical and pharmaceutical manufacturing plants indicated that male workers developed gynecomastia and female workers experienced intermenstrual bleeding. It has been documented that women taking oral contraceptives have an increased risk of thromboembolism, cerebral vascular disease, and myocardial infarction. It has also been noted that estrogens may be carcinogens (e.g., increased incidence of endometrial cancer among women on estrogen replacement therapy. DES is a transplacental carcinogen/teratogen to the offsprings).

A cross-sectional medical/industrial hygiene study has been initiated to study health problems of workers exposed to estrogens and to attempt to determine a safe level of exposure to these agents. During the second quarter of FY 78, a workshop was held (in lieu of the tripartite meeting) which was attended by representatives of the pharmaceutical manufacturing plants and a substantial amount of information was collected on manufacturing processes, employee profiles, etc. Five of these plants were selected for in-depth study; four of these manufacture oral contraceptives using synthetic estrogens and one proccesses conjugated estrogens of natural origin. It was also determined that there is no longer a plant in the U.S. which chemically manufactures DES in bulk and that pharmaceutical preparations containing DES are manufactured only sporadically. Because of this, it was decided that occupational effects of DES exposure will not be studied in this project. Feasibility determinations regarding the mortality study of workers occupationally exposed to products containing estrogens have been completed in all but one plant. The remaining company has been contacted and a walk-through survey date is being negotiated.

2. ENDOGENOUS HORMONES AND GYNECOLOGICAL CANCERS

32. ENDOCRINE CONTROL AND STEROID METABOLISM IN WOMEN WITH ENDOMETRIAL CANCER

Flamigni, C., Jasonni, V. M., Lodi, S., Bolelli, G. F., Universita degli Studi di Bologna, Fisiopatologia della Riproduzione, *Via Zamboni 33, 40126 Bologna, Italy*

The peripheral steroid metabolism, especially the production of extraglandular estrogens, was studied in vitro and in vivo in post-menopausal obese (n.4) and non-obese (n.2) women with and without endometrial cancer, and in women (n.3) with regular menses. Incubations, with Androstenedione as carrier, of adipose tissue (n.27), myometrium (n.11), endometrium (n.4), myomata (n.3) and abdominal skin (n.2) were performed with different techniques. No significant differences between obese and non-obese women, with and without endometrial cancer, were found. In all experiences a low aromatase activity was observed; different techniques, however, lead to different results. The in vivo production and conversion rate of Androstenedione and Estrone are continuing in 3 of the subjects.

A method to determine the bound-free fraction of steroids in blood was worked out in our laboratory for Androstenedione, Estradiol and Progesterone.

33. HORMONE DYNAMICS AND TARGET ORGANS IN AGING MEN AND WOMEN

Porter, J. C., MacDonald, P. C., Johnston, J. M., Wilson, J. D., Aiman, E. J., Barnea, A., Edman, C. D., Parker, C. R., University of Texas, Health Science Center at Dallas, Southwestern Medical School, Dept. of Obstetrics & Gynecology, *5323 Harry Hines Blvd., Dallas, Texas*, 75230, United States of America

The objectives of this Program Project are to determine the qualitative and quantitiative alterations in the sex hormone production profiles that occur in postmenopausal women and in aging men. In postmenopausal women, the dominant aspect of the sex hormone production profile is the extraglandular formation of estrone in association with decreased secretion of estradiol. In aging men, the dominant aspect of the sex hormone production profile is decreased secretion of testosterone in association with increased capacity for extraglandular estrogen formation. Moreover, in aging men and women, extraglandular estrogen formation is increased in the last third of life by obesity, age, and hepatic disease. At the same time, several degenerative or neoplastic diseases occur in hormone target tissues and organs. For example, in postmenopausal women, increased estrone production is associated with the occurrence of endometrial neoplasia. In men, the aging process is associated with prostatic hypertrophy and/or carcinoma. The occurrence of hot flashes at menopause indicates the involvement of the central nervous system and the vasculature. We propose to determine the production rates of sex hormones in postmenopausal women and in aging men and to determine the characteristics of those sex hormone production profiles that affect: (1) Lipid biosynthesis, (2) endometrial neoplasia and prostatic hypertrophy, (3) neuroendocrine function of the brain (especially the hypothalamus), and (4) release of gonadotropins and prolactin.

BIBLIOGRAPHIC REFERENCES: Bates, G. W., C. D. Edman, J. C. Porter, J. M. Johnston, and P. C. MacDonald, An assay for human erythrocyte catechol-O-methyl transferase activity using a catechol estrogen as the substrate, Clinical Chem. Acta 94: 63-71, 1979. Bates, G. W., C. D. Edman, J. C. Porter, and P. C. MacDonald, Catechol-O-methyltransferase activity in erythrocytes of women taking oral contraceptive steroids, Am. J. Obstet. Gynecol. 133: 691-693, 1979.

34. ANDROGEN AND ESTROGEN METABOLISM IN POSTMENOPAUSAL WOMEN WITH ENDOMETRIAL CANCER

Judd, H. L., University of California, Los Angeles Campus, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

This is part of a broader project. A summary of this subproject is not available.

35. ESTROGEN AND ANDROGEN STUDIES IN ENDOMETRIAL CANCER

Judd, H. L., LaGasse, L. D., Barone, R. M., Pilch, Y. H., University of California, Los Angeles Campus, School of Medicine, Dept. of Obstetrics & Gynecology, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

Adenocarcinoma of the endometrium occurs principally in postmenopausal women. Numerous studies have been published both for and against the association of abnormal estrogen metabolism with the development of this tumor. This research protocol proposes to comprehensively evaluate in vivo estrogen metabolism in postmenopausal women with endometrial cancer and in weight- and age-matched controls. The major androgenic precursors of estrogens will also be examined. The following studies will be performed in these patients: 1) The serum levels of estrone, estradiol, androstenedione and testosterone will be measured. 2) The metabolic clearance rates and production rates of the same estrogens and androgens will be quantitated. 3) The methods currently used to measure the peripheral conversion of androstenedione to estrone will be critically evaluated, and the best method for evaluating this important metabolic process will be adopted. 4) Circulation sex hormone binding globulin and free estradiol levels will be quantitated. 5) The histology and stage of the tumors will be correlated with the endocrine results.

It is also proposed that the extent of direct secretion of estrogens by the adrenal glands be assessed. Finally, the role of peripheral aromatization of androstenedione will be evaluated with the use of an in vivo inhibitor of this process.

BIBLIOGRAPHIC REFERENCES: Judd, H.L.: The endocrinology of polycystic ovarian disease. Clinical Obstetrics and Gynecology 21: 99, 1978. Lasley, B.L., Judd, H.L.: Pathophysiology of anovulation. Clinical Obstetrics and Gynecology 21: 87, 1978.

36. ESTROGEN METABOLISM IN PATIENTS WITH ENDOMETRIAL CARCINOMA - EFFECT OF MEDROXYPROGESTERONE ON THE PROGNOSIS OF ENDOMETRIAL CARCINOMA

Gronoos, M., Klemi, P. J., Rauramo, L., Punnonen, R., University Central Hospital of Turku, Dept. of Obstetrics & Gynecology, *SF20520 Turku 52, Finland*

We are investigating the secretory capacity, with regard to various steroids, of the ovaries of postmenopausal women with or without endometrial carcinoma using chemical, enzyme histochemical and ultrastructural methods. The plasma levels are measured in ovarian and cubital veins. The studies are in progress.

This is an old project and is organized together with the Departments of Obstet. and Gynec. of Helsinki and Oulu. The results are now under analysis.

37. COMPARATIVE STUDY OF HORMONAL LEVELS IN POST-MENOPAUSAL ENDOMETRIAL CANCER PATIENTS AND IN CASES WITH BENIGN CHANGES

Bremond, A. G., Mikaelian, S., Rochet, Y., Hopital Edouard Herriot, Clinique Gynecologique, *Pl. d'Arsonval, 69374 Lyon Cedex 2, France*

The assessment of hormonal patterns in post-menopausal women after a surgical operation for endometrial cancer will help to define the risk factors for that cancer. Follicle stimulating hormone, luteinizing hormone and prolactin are determined in the peripheral blood of cancer cases and controls, and 5-androstenedione, testosterone, estradiol and progesterone are also measured in the blood of the ovarian vein.

38. BINDING AND METABOLISM OF ANDROGENS IN PROSTATIC AND ENDOMETRIAL CANCER

Djoseland, O., Hoglo, S., Lunde, O., Bjoro, K., Haugen, H. N., Universitetet i Oslo, Rikshospitalet, Laboratories of Endocrinology/Reproduction/Medicine, *Oslo, Norway*

OBJECTIVE: To clarify any differences in the binding and metabolism of androgen hormones in human prostatic and endometrial tumors, as compared with normal tissue.

APPROACH: In order to study androgen receptors, the tissue is homogenized and centrifuged at 105,000 xg, 2 degrees C for 30 min. The specific receptor-binder R1881 is added to the cytosol in order to measure the androgen receptor concentration.

Total metabolism is measured by incubating tissue with tritiated testosterone, DHT or 5 alpha-androstane-3 alpha, 17 beta-diol, tris-buffer, pH 7.0, 37 degrees C for 30 min. The percentage distribution of the formed metabolites between water and diethylether is calculated after TLC.

Three androgen metabolizing enzymes are determined after homogenization and measurement of protein content. The activity of the 17 beta-hydroxysteroid dehydrogenase is measured after adding tritiated testosterone and measuring the amount of androstenedione formed. The 5 alpha-reductase activity is determined by incubating testosterone and measuring the total amount of DHT and 3 alpha-diol formed. Measurement of the activity of 3 alpha-hydroxysteroid dehydrogenase is performed by incubating DHT and determining the amount of 3 alpha-diol formed.

PROGRESS: Tissue from prostatic hyperplasia has a much higher 5 alpha-reductase activity than normal prostatic tissue, which in turn has a higher enzyme activity than tissue from well differentiated carcinoma. The prostatic 3 alpha-hydroxysteroid dehydrogenase activity in hyperplasia and carcinoma is approximately half of that found in normal tissue. Tissue from normal endometrium contains androgen metabolizing enzymes.

39. RADIOIMMUNOASSAY OF PITUITARY AND CHORIONIC GONADOTROPIN IN ENDOMETRIAL CANCER

Lewis, J. L., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

40. A SEROEPIDEMIOLOGIC STUDY OF ENDOGENOUS SEX HORMONES IN NEOPLASTIC DISEASE OF THE ENDOMETRIUM

Woolever, C. A., Bhavnani, B. R., Clarke, E. A., McMaster University, School of Medicine, Dept. of Obstetrics & Gynecology, *1200 Main St. W., Hamilton, Ontario*, L8S 4J9, Canada

We will determine the serum concentration of sex hormones in three groups of women, i.e., those having a recent diagnosis of carcinoma of the endometrium, hyperplasia of the endometrium and no endometrial disease. Serum samples are obtained from women who have had a recent histologic diagnosis of these conditions, as well as from a control population of age-matched women living in the same neighborhood as the cases. The samples are being analyzed for androstenedione, estrone, estradiol, estriol and their conjugates. Intergroup comparisons will be made with respect to the presence and absence of recent disease and the use of exogenous estrogens. Sample collection will be completed in April 1979 and the analyses by the end of the grant year.

41. OESTROGEN PRODUCTION IN FEMALE CANCER PATIENTS

James, V. H., Jacobs, H., Reed, M., University of London, St. Mary's Hospital Medical School, Dept. of Chemical Pathology, *Norfolk Pl., London W2 1PG, England, United Kingdom*

OBJECTIVE: We are trying to define the importance of the peripheral production of oestrogens in women in relation to the development of cancer.

APPROACH: Two groups of women are being studied; One control group and another group with endometrial cancer. In these two groups of women, we are comparing 24-hour profiles of plasma steroid and gonadotrophin levels, and by using isotope infusion techniques, we are investigating the production in the periphery and by secretion of oestrogens. We are seeking to confirm that the production of oestrogen from androgen changes with age and in relation to weight, and we are seeking to define the factors which influence this process both in cancer patients and in the control subjects. In addition, we are examining the production of oestrogens and the storage of steroid hormones in in vitro experiments using adipose tissue.

PROGRESS: To date, we have completed a series of studies defining the pattern of plasma steroid levels in normal subjects and in some patients with cancer. We have also completed a limited number of studies which suggest that the conversion of androgen to oestrogen is different in older patients as compared with younger females, and also that the metabolic pathways for androgen and oestrogen may be substantially different in relation to age.

42. ROLE OF ADRENAL CORTEX IN THE ETIOLOGY OF ENDOMETRIAL CANCER

IngelmanSundberg, A., Brody, S., Carlstrom, K., Lunell, N. O., Lagrelius, A., Rosenborg, L., Sabbatsberg Sjukhuset, Dept. of Obstetrics and Gynecology, *Dalagatan 9-11, Stockholm, Sweden*

The high frequency of adrenal hyperplasia in women with endometrial carcinoma is well-known and we have recently demonstrated increased levels of total oestrone as well as of the adrenal androgen dehydroepiandrosterone sulphate in postmenopausal women with endometrial carcinoma. In the proposed project we plan to investigate possible correlation between adrenal production of androgens and peripheral conversion into oestrogens on the one hand and endometrial carcinoma on the other hand.

43. ENDOCRINE RELATED FACTORS IN PATHOGENESIS OF ENDOMETRIAL CANCER (HUMAN)

Lucas, W. E., University of California, San Diego Campus, School of Medicine, Dept. of Medicine, *P.O. Box 109, La Jolla, California*, 92093, United States of America

This is part of a broader project. A summary of this subproject is not available.

44. ENDOMETRIAL CANCER AND CONJUGATED ESTROGENS IN OLMSTED COUNTY, MINNESOTA

Annegers, J. F., Mayo Foundation, Dept. of Medical Statistics & Epidemiology, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

This is part of a broader project. A summary of this subproject is not available.

45. SPECIALIZED CENTER FOR CANCER ENDOCRINOLOGY

Fishman, J., Kappas, A., Bradlow, H. L., Fishman, J. H., Martucci, C., Norton, B., Ikegawa, S., Tsukamoto, T., Fukushima, D. K., Rosenfeld, R. S., O'Connor, J. F., Lewis, J. L., Rockefeller University, University Hospital, *66th & York Ave., New York, New York*, 10021, United States of America

Radiometric studies on the biosynthesis and principal metabolic pathways of estrogen and androgens in patients with breast, endometrial and prostate cancer will be continued and the results compared with those obtained in normal subjects. The impact of endocrine therapy on these transformations will be followed to determine whether any correlations exist. The properties of receptors in human breast, endometrial and ovarian tumor tissues will be explored, with particular emphasis on the heterogeneity of these receptors. These differences in receptor properties will be correlated with the clinical history of the patients.

Studies on the pathways of estradiol biosynthesis and on the role of its transformation products produced in situ on the biological responses observed in various target sites will also be continued.

The mechanisms of formation and the role of the novel cortoic acids will remain an active area of study. New methods for the quantitation of these compounds are being explored.

Studies on the mechanism of entry of hormones into human breast cysts will be continued.

Studies of the influence of drugs and diet on the metabolism of estradiol in normal patients will be carried out to determine the influence of these compounds on the pathways of metabolism of estradiol in order to seek a relationship between diet or drugs and cancer risk.

BIBLIOGRAPHIC REFERENCES: 6-Aminoalkyl catechol estrogens - Models of steroidal biogenic amines. A. Takadate and J. Fishman, J. Org. Chem. 44: 67, 1979. Low urinary estrogen glucuronides in women at risk for familial breast cancer. J. Fishman, D. Fukushima and H. Lynch, Science 204: 1089, 1979.

46. MELATONIN STUDIES IN HUMANS

Lewy, A., Goodwin, F. K., Wehr, T., Gold, P., Potter, W., Markey, S., Kopin, I. J., Mendelson, W., Tamarkin, L., Cutler, N., Newsome, D., U.S. Dept. of Health & Human Services, Public Health Service, Alcohol Drug Abuse & Mental Health Admin., National Inst. of Mental Health, Clinical Psychobiology Branch, *Bethesda, Maryland*, 20014, United States of America

The role of the pineal gland and its hormone, melatonin, has been difficult to define in humans because the circulating levels of melatonin have been too low to measure. Recently, in collaboration with Dr. S. Markey of the LCS, we have developed a highly sensitive and specific (GC-MS) assay which requires less than 1 ml of human plasma, CSF, or urine. Since the development of this assay, melatonin research has been extended into two broad areas: (1) Investigation of the pattern of secretion of melatonin as affected by circadian, seasonal, and menstrual rhythm; the effect of light, drugs, and sleep; and in various pathologic syndromes (precocious puberty, delayed onset of puberty, infertility, hypothalamic, pituitary, adrenal, and thyroid diseases, hypertension, breast and ovarian malignancies, as well as affective disorders and schizophrenia). (2) Investigations of this hormone as a 'marker' for (a) the biologic 'clock', and (b) beta-adrenergic receptor function. We have found that sunlight, but not artificial light of normal intensity, suppresses melatonin secretion in humans, that melatonin is increased in mania and decreased in depression, that chronic tricyclic antidepressant treatment reduces melatonin, and that propranolol (a beta-adrenergic antagonist) abolishes melatonin secretion.

BIBLIOGRAPHIC REFERENCES: Markey, S.P. and Lewy, A.J.: Quantitative analysis of melatonin in human plasma by negative chemical ionization mass spectrometry. Proc. Ninth Materials Research Symposium. National Bureau of Standards, Special Publication 519, Trace Organic Analysis: A New Frontier in Analytical Chemistry, 1979, pp. 399-404.

47. MECHANISMS OF HORMONE DEPENDENCE OF HUMAN MALIGNANCY

Lippman, M. E., Monaco, M. E., Chong, M. T., Bronzert, D., Cowan, K., Lacroix, A., Tamarkin, L., Chabner, B., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Medical Breast Cancer Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

We are investigating the mechanisms whereby steroid and polypeptide hormones stimulate growth and specific protein synthesis in human breast cancer both in tissue culture model systems we have established and in clinical settings. A) We are studying the prevalency and clinical correlates of specific steroid receptors for estrogen, androgen, glucocorticoid and progesterone in human breast cancer, lymphomatous disease, melanoma, colon carcinoma, ovarian cancer and male breast cancer. B) Assays for specific gene products (alpha-lactalbumin, casein, fatty acid, synthetase, thymidine kinase) have been developed and we are studying the effects of steroid hormones, insulin and vasopressin on the activities and synthesis of these proteins.

BIBLIOGRAPHIC REFERENCES: Koeffler, H.P., Golde, D.W. and Lippman, M.E.: Glucocorticoid sensitivity and receptors in cells of human myelogenous leukemia lines. Cancer Res. 40: 563-566, 1980. Lacroix, A. and Lippman, M.E.: Binding of retinoids to human breast cancer cell lines and their effects on cell growth. J. Clin. Invest. 65: 586-591, 1980.

48. ESTROGEN PROFILES IN RELATION TO OVARIAN TUMORS AND UTERINE CANCER

Brown, J. B., Quinn, M., Pepperell, R. J., University of Melbourne, Obstetrics & Gynaecology, *Grattan St., Parkville, Victoria 3052, Australia*

OBJECTIVES: (a) To determine etiological factors related to estrogen production and metabolism which may predispose to ovarian and uterine cancer. (b) To formulate methods of reducing the incidence of these cancers. (c) To develop hormone screening tests to identify women at risk.

APPROACH: Measurement of several estrogen metabolites in urine and several androgens and estrogens in serum of postmenopausal women with high risk conditions, e.g., atypical hyperplasia of the endometrium and obesity, and compare the values with those seen in postmenopausal cases and controls.

PROGRESS: Women with atypical hyperplasia of the endometrium requiring hysterectomy have higher estrogen values than women with carcinoma of the endometrium; this estrogen is derived from the ovaries and the structures involved are being investigated. Approximately 40-50% of patients with endometrial cancer have higher estrogen values than the controls; this estrogen is not of ovarian origin. A much larger series of cases and controls is now being studied.

3. HORMONAL INDUCTION OF EXPERIMENTAL GYNECOLOGICAL CANCERS

49. HORMONAL CONTROL OF NORMAL AND TUMOR CELLS

Auricchio, F., Rotondi, A., Migliaccio, A., Schiavone, E., La Storia, S., Castoria, G., Universita degli Studi di Napoli, Fac. di Medicina e Chirurgia, *via Orazio 31, 80100 Naples, Italy*

OBJECTIVE: The objective of the present research is the identification of the process responsible for the rapid nuclear loss of the estradiol-receptor complex observed in vivo. The nuclear loss of the receptor seems in fact related to the estradiol responsiveness of estrogen target tissues.

APPROACH: It is essentially a biochemical approach. The work is directed toward identification, purification and characterization of the nuclear activity responsible for the nuclear receptor inactivation. The activity will be purified and tested on pure estradiol receptor to study the receptor inactivating mechanism. Activators and inhibitors of the receptor inactivating activity will be used to modify the estrogen dependence of target tissues and to assess the physiological role of this activity.

PROGRESS: A nuclear activity inactivating the cytosol, as well as the nuclear estradiol receptor, has been identified in uterus and mammary gland of mouse. This activity is specific to estrogen dependent tissues.

50. INFLUENCE OF PERINATAL ALTERATIONS ON CARCINOGENESIS

Nishizuka, Y., Aichi Cancer Center Research Inst., *81 1159 Kanokoden Tashiro-cho, Chikusa-ku, Nagoya 464, Aichi, Japan*

Exposure to abnormal stimulation during the perinatal period may cause profound cellular and/or tissue alterations which often persist and may somehow be connected with tumor development in later life. This contract is primarily concerned with effects of hormonal and immunological imbalances at this particular age, and consists of two systems using mice and rats 1) to investigate the mechanism of development and nature of permanent alterations of the vagina and coagulating gland after perinatal exposure to steroids and the possible correlation to carcinogenesis; and 2) to investigate the mechanism of development and nature of autoimmune disorders, mostly focusing on oophoritis, and the possible correlation to tumorigenesis in neonatally thymectomized mice.

51. DOSE-RESPONSE CARCINOGENIC ESTROGENIC BIOASSAYS WITH C3H/HEN MICE UNDER SPECIFIC PATHOGEN FREE/DEFINED FLORA (SPF/DF) CONDITIONS

Norvell, M. J., U.S. Dept. of Health & Human Services, Public Health Service, Food & Drug Admin., National Center for Toxicological Research, Division of Molecular Biology, *Jefferson, Arkansas*, 72079, United States of America

OBJECTIVE: Quantitatively compare the effects of continuous feeding of graded levels of DES on uterine-cervical lesions and mammary tumorigenesis in C3H mice.

TEST COMPOUND: DES (Diethylstilbestrol).

TEST ORGANISM: Exp. 078 - Rodent, mouse, C3H/HeN MTV positive. Exp. 079 - Rodent, mouse, C3H/HeN MTV negative.

ROUTE OF ADMINISTRATION: Dosed feed.

DURATION OF EXPOSURE: Continuous feeding ad libitum.

TEST PARAMETERS: Histopathology, blood chemistries.

52. EFFECTS OF INTRAUTERINE EXPOSURE TO DIETHYLSTILBESTROL (PRIMATES)

Herbst, A. L., Harvard University, Boston Campus, School of Medicine, Dept. of Obstetrics & Gynecology, *25 Shattuck St., Boston, Massachusetts*, 02115, United States of America

This is part of a broader project. A summary of this subproject is not available.

53. TRANSPLACENTAL CARCINOGENESIS

Miller, R. K., Baggs, R. B., University of Rochester, School of Medicine & Dentistry, Dept. of Obstetrics & Gynecology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

The objectives of this project are 1) to establish a model for transplacental carcinogenesis in the rat using diethylstilbestrol (DES) and comparing it with natural estrogens, and 2) to identify the mechanisms of this chemically induced carcinogenesis due to prenatal exposure.

In the prenatally exposed DES Wistar rat population (0.1 to 50 mg/kg), 38% of the female progeny (120) and 74% of the male progeny (157) have demonstrated teratogenic, dysplastic, metaplastic, or neoplastic lesions. A 9-10% incidence of non-neoplastic lesions was observed in our control population (116). A dose-effect relationship was noted in the progeny when the diethylstilbestrol was administered on days 18, 19, and 20 of gestation.

Metabolism of DES by fetal rat tissues has been demonstrated utilizing in vitro as well as in vivo technics. Besides oxidative and glucuronide metabolites, 4-10% (depending upon the particular tissue studied) of the total tissue radioactivity originally associated with 14C-DES is covalently bound to cellular components. Under in vitro conditions, oxygen is required for this covalent binding of DES/metabolites and trichloropropene oxide (an inhibitor of epoxide hydrase and glutathione) increased the covalent binding. Metyrapone did not substantially decrease this binding while 4 degrees C incubation markedly inhibited binding. Thus, metabolism of DES to reactive intermediates, e.g., epoxides, quinones, is critical for this covalent binding in tissue sections both in the fetus and in the mother. Modification of the terato/tumorigenicity utilizing these biochemical observations is in progress.

BIBLIOGRAPHIC REFERENCES: R.K. Miller and R.C. McKenzie, Diethylstilbestrol and Estradiol Binding to Fetal and Maternal Tissues: Role of Metabolism, Society for Gynecologic Investigation, San Diego, Calif., March 1979. R.K. Miller and R.C. McKenzie, The Role of Diethylstilbestrol Metabolism in its Binding to Fetal and Maternal Tissues, Fed. Proc. 38:439, 1979.

54. AGING EFFECTS ON OVARIAN TUMORIGENESIS

Johnson, D. C., Cheng, H. C., University of Kansas, Medical Center, School of Medicine, Dept. of Obstetrics & Gynecology, *39th St. & Rainbow Blvd., Kansas City, Kansas,* 66103, United States of America

The project involves two problems of aging of the reproductive system. First is whether steroidal insults to the central nervous system during a critical period in development can cause premature aging of the hypothalamic-hypophysial-ovarian axis. The second question is whether aging of the ovary induces a susceptibility to tumor formation or whether tumors are formed only because of a change in the endocrine environment associated with aging in higher control centers. These problems are being studied by exposing rats to various doses of steroids during the first 10 days postnatally. The cyclic pattern of ovarian function in these animals will then be followed over a period of months. At various times after cyclic function ceases (aged animals) ovaries will be exposed to an environment known to rapidly induce tumors. The test system involves transplantation of ovaries into male parabiotic partners of castrate males; thus the ovary is constantly exposed to high levels of follicle stimulating and luteinizing hormone. With this system we will compare endocrine functions and progress of tumor formation in 'old' ovaries which have functioned normally for long periods to that of 'young' ovaries which have undergone few cycles. Immunoassays of gonadotropins, as well as steroids, will be used to evaluate functional changes in the ovaries with aging.

55. STUDIES OF THE ACTIONS OF GONADOTROPINS ON OVARIAN TUMORS

Kammerman, S., New York University, School of Medicine, Dept. of Medicine, *550 1st Ave., New York, New York,* 10016, United States of America

The broad objective of the proposed research is to characterize the interaction of gonadotropic hormones including luteinizing hormone (LH), follicle stimulating hormone (FSH), and human chorionic gonadotropin (hCG) with ovarian tumor tissue. The goal is first to define the role and mechanism of action of gonadotropins in the pathogenesis and maintenance of ovarian tumors and second to define in vitro biochemical parameters of the neoplasms which may be related to their pathological behavior in vivo.

An animal model for ovarian tumorigenesis will be studied, as well as a variety of human pathological specimens. Hormone binding, molecular biologic response, hormone chemistry and receptor isolation will all be studied.

It is hoped that these studies will have multiple benefits in defining the pathologic role and molecular mechanism of gonadotropin action in ovarian tumors, in delineating biochemical characteristics of the tumors that could be used to develop diagnostic and prognostic criteria in patient management and in providing basic information on the regulatory mechanisms involved in reproductive physiology and ovarian maturation.

56. PITUITARY CONTROL OF OVARIAN FOLLICULAR GROWTH

Schwartz, N. B., Northwestern University, Chicago Campus, School of Medicine, Dept. of Biological Sciences, *303 E. Chicago Ave., Chicago, Illinois,* 60611, United States of America

This is part of a broader project. A summary of this subproject is not available.

57. EFFECT OF ESTROGEN ON NORMAL AND ABNORMAL CELL GROWTH

Clark, J. H., Hardin, J. W., Baylor College of Medicine, School of Medicine, Dept. of Cell Biology, *1200 Moursund Ave., Houston, Texas,* 77025, United States of America

Neonatal administration of either of the non-steroidal estrogen antagonists, Nafoxidine and Clomid, causes a hyperestrogenization syndrome which results in the production of abnormalities of the reproductive tract of the adult rat. These abnormalities include preneoplastic and neoplastic lesions. The histopathology of this syndrome will be further examined and the ability of various estrogens to induce it will be compared. The developmental sequence and preneoplastic changes that occur in the reproductive tract and other estrogen sensitive tissues will be examined. The effect of neonatal estrogen stimulation on reproductive physiology of the animals will be examined by measuring steroid and gonadotropin hormones in the blood during development. Hyperestrogenization also stimulates the formation of nuclear bodies in uterine epithelial cells. The formation of these nuclear bodies will be studied in relation to estrogen receptor binding, transcriptional activity and abnormal cell development. The ability of progesterone to inhibit nuclear body formation and abnormal cell growth will also be examined. The nuclear bodies will be characterized by enzymatic and autoradiographic methods. Isolation will be done by differential gradient centrifugation and gel filtration. Further characterization of the nuclear bodies will be undertaken by direct biochemical analysis and cDNA hybridization. Estrogen receptor binding to nuclear bodies will be related to other nuclear compartments.

4. HORMONE RECEPTORS AND GYNECOLOGICAL CANCERS

58. AN INVESTIGATION OF STEROID RECEPTORS IN NORMAL, PREMALIGNANT AND MALIGNANT HUMAN ENDOMETRIUM

Utaaker, E., Stoa, K. F., Iversen, D. E., Segadal, E., Universitet i Bergen, Hormone Lab., *Haukeland Sykehus, Postboks 1, 5016 Bergen, Norway*

OBJECTIVE: The clinical use of steroid receptor determinations in normal, premalignant and malignant human endometrium will be investigated in samples from a relatively large number of patients. The results will be compared with clinical data, such as the effect of hormone treatment, hormone assays in plasma and histological and cytological examinations of the tissue.

APPROACH: The Department of Obstetrics and Gynecology at the University Hospital in Bergen has for the first time in Norway adopted a new, not very traumatic aspiration method for endometrium diagnostics. The present project aims at working out and examining methods for estrogen and progesterone receptor investigation in these aspirates. As a supplement to these studies, we plan to measure the activity of different enzymes, such as estrogen sulfatase and 17beta-hydroxysteroid dehydrogenase, in the aspirates.

59. STEROID HORMONE RECEPTORS IN HUMAN HORMONE-SENSITIVE TUMORS

Galli, M. C., DeGiovanni, C., Grilli, S., Universita degli Studi di Bologna, Istituto di Cancerologia, *via S. Giacomo 14, 40126 Bologna, Italy*

OBJECTIVE: To test a correlation between the presence of estrogen, androgen, progestin and/or glucocorticoid receptors in human hormone-sensitive tumors and the response rate to endocrine treatment.

APPROACH: Cytoplasmic steroid receptors are determined using a slightly modified dextan-coated charcoal (DCC) method (Cancer Lett. 2, 247-158, 1977; IRCS Med. Sci., 6, 418, 1978) in breast, prostate, endometrium, kidney and ovary cancer and related normal tissues. Hormonal plasma levels and histochemical parameters such as: grading, elastosis, casein production, etc., are determined and clinical data are collected.

PROGRESS: Up to now steroid hormone receptors have been determined in about 200 breast specimens, 50 prostate specimens, 100 endometrial biopsies and 20 cases of kidney tumor and 20 cases of ovary neoplasm. Interestingly, estrogen, androgen, progestin and glucocorticoid receptors are present also in normal and neoplastic ovary.

60. STEROID HORMONE RECEPTORS AND CIRCULATING HORMONE LEVELS IN GYNECOLOGICAL MALIGNANCIES

Kauppila, A., Vihko, R., Janne, O., Syrjala, P., Oulu University Central Hospital, Dept. of Obstetrics & Gynecology, *Kajaanintie 51, 90220 Oulu 22, Finland*

OBJECTIVE: To determine the cytoplasmic and nuclear receptor binding sites for estradiol and progesterone in endometrial and ovarian malignancies. The clinical value of these results in the treatment of endometrial carcinomas with high-dose progestogens will be evaluated. Also, the possible importance of receptor induction will be evaluated.

APPROACH: The estrogen and progesterone receptor measurements were performed with a dextran-coated charcoal technique and sucrose density gradient centrifugation. Serum estradiol, progesterone, LH, FSH and prolactin levels were determined by radioimmunoassay.

PROGRESS: Until now about 150 gynecological malignancies have been studied. The results have been presented in the 2nd International Meeting on Endometrial Cancer and Related Subjects, London, 30-31st March, 1977 (Abstracts) and in XVI Nordiska Kongressen for Klinisk Kemi och Klinisk Fysiologi, Oulu 28-30.6. 1977 (Abstracts, p. 81). Syrjala, P., Kontula, K., Janne, O., Kauppila, A., and Vihko, R.: Steroid receptors in normal and neoplastic human uterine tissue. In Gynecological Malignancy. Eds. Brusch, M.G., Taylor, R.W. and King, R.J.B. Bailliere Tindall, London, 1978, in press. R. Vihko was a joint author of chapter Receptors for steroids in human endometrium. In Hormonal biology of endometrial cancer. A series of workshops on the biology of human cancer. Report No 8. Eds. Richarson, G.S. and MacLauglin, D.T., International union against cancer. Technical Report Series, Vol. 42, 63-112, 1978.

This project will continue for 3-5 years.

61. ESTROGEN AND PROGESTERONE RECEPTORS, TISSUE AND PLASMA ESTRADIOL AND PROGESTERONE IN ENDOMETRIAL AND BREAST CANCER (ABBREV)

Hahnel, R., Ratajczak, T., Twaddle, E., University of Western Australia, King Edward Memorial Hospital for Women, Dept. of Obstetrics & Gynaecology, *Subiaco, W. Australia 6008, Australia*

OBJECTIVE: To determine the relationship between hormone receptors, circulating hormone levels and hormone concentrations in the tissue.

APPROACH: Measurement of estrogen and progesterone receptors in the tumor tissues of patients with endometrial or breast cancer; measurement of estradiol and progesterone in the tumor homogenates and in the cytosols; measurement of estradiol, estrone, progesterone, testosterone and SHBG in blood. Correlation of all results.

PROGRESS: In endometrial carcinoma the mean levels of SHBG were significantly higher in ER-positive than in ER-negative carcinomas.

62. HORMONE RECEPTORS IN HUMAN ENDOMETRIAL CARCINOMA

Hahnel, R., Ratajczak, T., Martin, J. D., University of Western Australia, King Edward Memorial Hospital for Women, Dept. of Obstetrics & Gynaecology, *Subiaco, W. Australia 6008, Australia*

OBJECTIVE: To determine the prognostic significance of estrogen and progesterone receptors in endometrial carcinoma.

APPROACH: Estimation of estrogen and progesterone receptors in cytosol and nuclear extract of endometrial cancer tissue. The data will be related to the disease-free period and the survival of the patients.

PROGRESS: Preliminary results indicate that the survival of patients with estrogen receptor-positive carcinomas is better than that of patients with estrogen receptor-negative carcinomas.

63. ISOLATION OF ESTRADIOL RECEPTOR FROM HUMAN UTERUS

Hahnel, R., Ratajczak, T., University of Western Australia, King Edward Memorial Hospital for Women, Dept. of Obstetrics & Gynaecology, *Subiaco, W. Australia 6008, Australia*

OBJECTIVE: To purify and isolate preparative quantities of the estradiol receptor from human uterus.

APPROACH: Removal of albumin and SHBG from receptor containing cytosol by specific adsorption. Purification of estradiol receptor by affinity chromatography. Use of bovine uterine receptor as a model for refinement of purification procedures before large-scale commitment of human tissue.

PROGRESS: Heparin Sepharose has been shown to interact with the estradiol receptors from human and calf uterus. The procedure completely eliminates albumin and to a large extent SHBG resulting in receptor preparations which are highly suitable for further purification by affinity chromatography. Purity increases of 7000- and 5000-fold have been obtained for the calf and human receptors respectively, with yields of 50 percent.

64. HISTOCHEMICAL DETERMINATION OF STEROID RECEPTORS IN GYNECOLOGICAL CANCERS

Lantta, M., Stenman, U., Helsingin Yliopisto, Hormon Lab., *Haartmaninkatu 2, c/o Hosp. of Obstetrics & Gynecology, SF00290 Helsinki 29, Finland*

OBJECTIVE: To develop a clinically useful method for determination of steroid receptors. The commonly used hormone receptor assays have certain limitations. Fairly large amounts of tissue are needed for reliable determinatons, and with the presently used methods it is not possible to correlate the receptor determination to the histological finding; therefore a reliable result is obtained only when the malignant tissue can be easily separated from adjacent normal tissue. We therefore aim at developing a histochemical method for determination of steroid receptors.

APPROACH: Steroid receptors in breast cancer have been determined by using steroid conjugates, fluoresceing antibodies and mixed fluorescein-steroid-conjugates. We will use mixed conjugates of fluorescein-steroid-bovine serum albumin (BSA) to determine steroid receptors in gynecological cancers. The results obtained by this histochemical method will be compared to those obtained by the classical biochemical assay. We have set up the isotope method for progesterone and estradiol receptors. For the histochemical determination we initially used polyestradiol-phosphate and fluorescent anti-estradiol antibodies. Because this method gives too high background fluorescence we have synthesized mixed conjugates of fluorescein, estradiol and BSA and corresponding conjugates of progesterone. We are now testing the specificity of the fluorescence by staining various tissues with these conjugates.

65. HORMONE DEPENDENCE IN ENDOMETRIAL AND BREAST CANCER

Giannopoulos, G., Davies, J. I., Knapp, R., Harvard University, Boston Campus, Boston Hospital for Women, Dept. of Obstetrics & Gynecology, *221 Longwood Ave., Boston, Massachusetts,* 02115, United States of America

The following investigations are proposed: 1. To quantitate the levels of estrogen and progesterone receptors in normal endometrium, hyperplastic endometrium, endometrial carcinoma, and breast carcinoma. The data will be used to evaluate the correlation of critical levels of estrogen and/or progesterone receptors in endometrial and breast tumors with the patients' response to endocrine therapy. 2. The association of estrogens with endometrial cancer will be examined by measuring estrone and estradiol levels in plasma, whole endometrial tissue and endometrial nuclei, as well as estrone-estradiol interconversions in the endometrium of patients with hyperplasia and carcinoma. 3. The mechanisms involved in the objective remission of endometrial tumors by progestational agents will be investigated by studying the following parameters in tumor tissue before and after progestin therapy: levels of estrogen receptors; levels of estrone and estradiol; estrone-estradiol interconversion; uptake and intracellular distribution of estrone and estradiol.

66. HORMONE RECEPTOR ONTOGENY AND CANCER

Leavitt, W. W., Worcester Foundation for Experimental Biology Inc., *222 Maple Ave., Shrewsbury, Massachusetts*, 01545, United States of America

Possible relationships between steroid-hormone receptors and the diethylstilbestrol (DES)-induced abnormalities of the cervix and vagina will be explored through the examination of the ontogeny of steroid-hormone receptors in these tissues when exposed to different steroid conditions. The quantity of estrogen and progesterone receptors in the cytosol (cRe, cRp) of mice and hamsters will be determined by Scatchard plot analysis; nuclear estrogen and progesterone receptors (nRe, nRp) will be measured by exchange assays. These receptors will also be characterized by sucrose-glycerol density gradients and competitive binding studies. The above receptor parameters will be measured during the ontogeny of the cervix and vagina in (1) normal, (2) vehicle-treated, (3) DES-treated, (4) ovariectomized and/or adrenalectomized and (5) progesterone-treated animals. The underlying hypothesis is that DES, when administered during early developmental stages, alters the quantity or binding qualities of Re and/or Rp and the hormone receptor-nuclear acceptor interactions in the cervix and vagina at later times.

67. HORMONE RECEPTORS AND PEROXIDASE IN NORMAL ENDOMETRIAL TISSUE AND ENDOMETRIAL CANCER

DeSombre, E. R., University of Chicago, Pritzker School of Medicine, Dept. of Obstetrics & Gynecology, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

This is part of a broader project. A summary of this subproject is not available.

68. HORMONE RECEPTORS AND PEROXIDASE ACTIVITY IN OVARIAN CANCER

Holt, J. A., University of Chicago, Pritzker School of Medicine, Dept. of Obstetrics & Gynecology, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

This is part of a broader project. A summary of this subproject is not available.

69. HORMONE PRODUCING NONENDOCRINE TUMORS

Samaan, N. A., Yang, K. P., Hill, C. S., Hickey, R. C., Ward, D. N., Rutledge, F. N., Smith, J. P., Blumenschein, G. R., Copeland, E. M., Jesse, R. H., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Medicine, *c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

Hormone production by nonendocrine tumors may serve as a marker for early detection. 1) Hormone production by nonendocrine tumors will be measured in peripheral circulation, in affluent and effluent blood obtained at catheterization under fluoroscopy or at surgery in tumor and control tissues. 2) The effects of various methods of therapy on hormone production with progression or regression of the disease will be determined. 3) The effect of certain cancers on hormone secretion by endocrine organs will be studied. 4) The endocrine disturbances which may result as side-effects of different methods of therapy of cancer will be studied. 5) Effect of parenteral hyperalimentation on circulating hormone levels will be evaluated. 6) On detection of hormone producing tumors, the tumors will be extracted directly or cultured in vitro to secrete the hormones. The substances thus obtained are then tested for their physical and chemical properties. Chemical and physical characterization including Sephadex gel- and ion-exchange chromatography will be conducted where practical to compare the molecular size of nonendocrine tumor hormones with native hormones. 7) Localization of hormone production by the tumor will be done by immunohistochemistry. 8) Identify and quantitate the specific hormone receptors in breast and endometrial carcinoma. 9) Investigate the effects of prolactin and other polypeptides and steroid hormones on the growth of breast cancer cells in culture. 10) Study the hormonal changes which might occur with adjuvant chemotherapy in treatment of breast cancer patients and correlate the course of the disease with the hormone profile in these patients.

70. CLINICAL-LAB STUDIES IN GYNECOLOGIC CANCER

Herbst, A. L., Ultmann, J. E., University of Chicago, Pritzker School of Medicine, Dept. of Obstetrics & Gynecology, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

This interdisciplinary collaborative investigation will allow coordinated research into the early identification, biologic behavior, and treatment of gynecologic cancers. Specific aims include: 1. Study steroid receptor content and peroxidase activity in normal, premalignant, and malignant endometrial tissue, characterize their relationships, and correlate these parameters with the patient response to hormonal therapy. 2. Study the biology of ovarian epithelial adenocarcinomas by determining their content and classes of hormone receptors and peroxidase activity and correlating these data with serum sex hormone levels, histologic grade and clinical characteristics of the tumor. 3. Ascertain if lithium carbonate can attenuate chemotherapy-induced neutropenia, and conduct in vitro studies on lithium carbonate to characterize its mechanism of action. 4a. Identify specific antigens, antibodies, and immune complexes associated with ovarian epithelial carcinomas for tumor detection and characterize immunologic and protein markers in patients with various types of gynecologic malignancies to correlate with tumor behavior. 4b. Develop sensitive assays for the tumor associated antigens and antibodies and assess these to diagnose and/or monitor ovarian cancer. 4c. Investigate certain aspects of the cellular immunologic reaction of the body to ovarian cancer. 4d. Produce rodent and human monoclonal antibodies against human ovarian epithelial cancer associated antigens which are important in the body's immune response to the tumor.

71. STUDY OF HORMONAL DEPENDENCE OF NEOPLASMS

Franchimont, P., Zangerle, P. F., Hendrick, J. C., Hustin, J., Laboratorium de Radioimmunologie, Tour de Pathologie, *C.H.U. Bat. B23, Sart-tilman, 4000 Liege, Belgium*

The purpose of this program is to define the hormonal dependence of tumors in organ culture. The cancers which will be studied in organ culture are: breast cancer; trophoblastic tumors; and endometrium carcinoma.

The influence of trophic hormones will be determined. They are polypeptidic hormones (growth hormone, somatomedins, somatostatin, insulin and prolactin) or steroid in nature (oestradiol and progesterone). Their effects will be analyzed after isolated or simulataneous addition to the culture.

Three groups of parameters will be studied: Identification and analysis of characteristics of receptors for these hormones; quantification of processes of cellular growth by labelled thymidine, uridine and leucine incorporation studies; production of all assayed tumor markers by cancerous cells: hormones; exocrine products; and embryonic antigens.

72. EFFECTS OF ANDROGENS AND METABOLISM OF STEROIDS IN A UTERINE CELL LINE

Eiknes, K. B., Bakke, O., Lamvik, J., Norges Tekniske Hogskole, Inst. of Biophysics, *Trondheim*, 7034, Norway

OBJECTIVE: To investigate the relationship between steroid receptors in cells from the human cell line NHIK 3025 and effects of steroids on growth of these cells.

APPROACH: The cell line NHIK 3025 originates from a uterine carcinoma and has been cultivated in vitro since 1967. Ultrastructure of these cells is similar to that of HeLa, with DNA content three times that of normal diploid cells and a chromosome number of 122 plus or minus 2. Growth of these cells is inhibited by glucocorticoids (prolongation of the cell cycle) and stimulated (shortening of cell cycle) by the androgens testosterone (T) or 4-androstene-3 beta, 17 beta-dio (delta 4-3 beta). Progesterone or estrogens have no effect on growth of these cells which possess a cytoplasmic receptor for T (binding 8-10 f.mol. T/mg protein) and a cytoplasmic receptor for glucocorticoids (binding 90 f.mol. dexamethazone/mg protein). The nuclei from these cells have a receptor binding T, delta 4-3 beta or dihydrotestosterone (DHT) at 110 f.mol. steroids/mg protein. DHT will not stimulate growth of these cells. The cells have no cytoplasmic or nuclear macromolecule associated with progesterone or the estrogens in a specific way. Cells are incubated with steroids and binding association, steroid metabolism and cell growth investigated employing synchronized and non-synchronized cell populations. Effects on these parameters are also being determined when the cells are cultured in media deficient in or lacking blood serum.

PROGRESS: The growth stimulating effect of T or delta 4-3 beta is lost when the cells are cultured in a steroid-free medium for 21 days. Dexamethazone will show inhibitory effect on cell growth when used on cells grown in a steroid-free medium for 21 days. Effects of dexamethazone on cell growth can be recorded within 2-3 hours after exposure and this steroid is equally active during [illegible] different phases of the cell cycle as if it were inactivating [illegible] growth principle contained in the medium. The nature of this possible inactivation process is currently being investigated.

73. METABOLIC STUDIES OF HUMAN UTERINE NEOPLASMS

Rose, L. I., Connor, J. S., Koffler, D., Hahnemann Medical College & Hospital, Medical College, Dept. of Medicine, *235 N. 15th St., Philadelphia, Pennsylvania*, 19102, United States of America

Comparisons of human uterine neoplasms with normal tissues have shown an increased rate of conversion of testosterone to its physiologically more active metabolite, dihydrotestosterone. In addition to these in vitro investigations, we have also identified a saturable cytoplasmic binding protein in both normal and neoplastic tissues. The androgen receptor concentrations are also elevated in the uterine neoplasms. The 5 alpha-reduction of testosterone and the specific binding of dihydrotestosterone constitute two important steps thought to be necessary for androgens to elicit tissue response. Furthermore, the elevated levels of both of these phenomena in the neoplasms studied suggest a physiologically significant role for androgens in uterine neoplastic disease.

BIBLIOGRAPHIC REFERENCES: Reddy, V.V., and L.I. Rose. Delta4-3-ketosteroid 5 alpha-reductase in human uterine leiomyoma. Am. J. Obs. & Gyn. 135:415. (1979).

74. STUDIES OF CARCINOGENESIS IN HUMAN TISSUE

Kaufman, D. G., University of North Carolina, Chapel Hill Campus, School of Medicine, Dept. of Pathology, *Manning Dr., Chapel Hill, North Carolina*, 27514, United States of America

OBJECTIVES: Develop methods for obtaining human endometrial tissue from normal patients and also for obtaining non-malignant endometrial organ cultures. Develop optimal techniques for maintaining human endometrial tissue in organ culture for prolonged periods (weeks or months); these efforts will be modeled upon preliminary studies employing endometrial and other tissue from experimental animals. Determine the morphologic characteristics of human endometrial organ cultures so as to confirm their similarity to normal endometrial tissue. Determine normal biological and biochemical properties of human endometrial tissue which may serve as alternate methods for evaluating normalcy of this tissue in culture. Subject human endometrial tissue in organ culture to chemical carcinogens and determine the extent and characteristics of the metabolic activation of these chemicals and their binding to the DNA in endometrial cells in culture.

75. STEROID DYNAMICS IN HUMAN ENDOMETRIAL CANCER

Gurpide, E., Gusberg, S. B., Fleming, H., City University of New York, Mount Sinai School of Medicine, Dept. of Obstetrics & Gynecology, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

Specimens of endometrial carcinoma will be used for in vitro studies involving organotypic cultures of tissue fragments, separation of glands from stromal elements, and cultures of monolayers of epithelial and stromal cells. Levels of enzymatic activities (e.g., 17-beta-hydroxysteroid dehydrogenase) and concentrations of estradiol and progesterone receptors will be measured in order to evaluate conditions necessary for the preservation and augmentation of these levels. Increment in 17-beta-dehydrogenase activity are a rather specific indicator of response of the tissue to progestins. Correlations between receptor levels, 17-beta-dehydrogenase activity, and in vitro responsiveness to progestins will be sought. In some cases, patients with endometrial carcinoma will receive medroxyprogesterone acetate for a few days in order to evaluate, morphologically and biochemically, in vivo effects of the progestin and compare them with results obtained in vitro with pretreatment specimens. Epithelial cells derived from the same specimens will be transplanted into hamsters and nude mice subjected to hormonal manipulations.

Other studies to be conducted on specimens of endometrial cancer include the measurement and characterization of the newly identified 'available' estrogen receptors in the endometrial nuclei, the assessment of hormonal influences on rates of pyrimidine synthesis, and quantitation of the uptake and metabolism of estrogens, androgens and progesterone, by superfusion of cell suspensions.

76. HUMAN ENDOMETRIAL CARCINOMA CELL CULTURES

Gurpide, E., City University of New York, Mount Sinai School of Medicine, School of Medicine, Dept. of Obstetrics & Gynecology, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

77. HORMONE PRODUCTION IN CULTURED CELLS

Kohler, P. O., Bordelon, M., Norris, J. S., University of Arkansas, Medical Sciences Campus, School of Medicine, Dept. of Medicine, *4301 W. Markham St., Little Rock, Arkansas*, 72201, United States of America

This application is for renewal of grant AM21458.

The overall objective of this project is to utilize model cell culture systems to study hormone synthesis by endocrine cells. The hormone-producing cells utilized for these studies include the JEG clonal lines of human choriocarcinoma cells which synthesize the glycoprotein hormone, chorionic gonadotropin, as well as another protein hormone, placental lactogen. These cells also produce progesterone and convert appropriate 19-carbon steroid percursors to estrone and estradiol. These choriocarcinoma cells will be used with new hybrid strains to be developed to map genes for hormone synthesis to specific human chromosomes.

The major techniques to be used to study hormone synthesis by the cells include: 1) Cell hybridization between hormone producing cells and non-endocrine mouse and human cells performed by fusing the cells and utilizing special selected media and cloning procedures to develop hybrid strains. Mutagenic agents will be used to alter hormone production in some parent and hybrid cells. 2) The modified strains will be examined for hormone production using chromatography and radioimmunoassays for measurement of hormones and protein hormone subunits. Steroid synthesis will be examined by radioimmunoassays which are specific for particular steroids and by conversion of specific labeled hormone precursors into steroids. Subsequent studies will be performed employing complementation techniques utilizing different hybrid clones for correction of enzyme deficiencies in the steroid synthetic pathways. 3) Nucleic acid hybridization studies will be performed with hybrid strains utilizing labeled DNA complementary to the mRNA's for the alpha and beta subunits of hCG to identify hybrids containing structural genes for chorionic gonadotropin subunits. 4) Chromosomal analysis will be performed on hybrid cells utilizing enzyme assays and special staining techniques. These studies will be used to assign genes for specific hormones and subunits and enzymes in the steroid synthetic pathways to specific chromosomes. The control of hormone synthesis will be examined in the modified cell strains.

BIBLIOGRAPHIC REFERENCES: Siciliano, M.J., M.R. Bordelon, and P.O. Kohler: Expression of Human Adenosine Deaminase (ADA) After Fusion of ADA Deficient Cells with Mouse Fibroblasts. Proc. Nat. Acad. Sci. 75:936, 1978.

78. BIOCHEMICAL AND CLINICAL ASPECTS OF STEROID RECEPTORS

Colas, A. E., Buchler, D. A., University of Wisconsin, Madison Campus, Medical School, Dept. of Obstetrics & Gynecology, *307 N. Charles St., Madison, Wisconsin*, 53706, United States of America

The macromolecules in mammalian uterine cytosols responsible for the high-affinity and specific binding of steroid hormones, in particular progestins and glucocorticoids, are the object of this study. Working with purified preparations, we intend to study the interactions of steroid receptor complexes with nuclear material, the relationship of these interactions to the biological effects of the hormones and the possible clinical value of receptor studies in the diagnostic and prognostic assessment of endometrial cancer. The uterine cytosols will be fractionated on spheroidal hydroxyapatite columns to separate the progestin-specific receptor from other high-affinity binding proteins. Endometrial cultures and suppression techniques will be used to study the nuclear interactions of receptor complexes and the hormonal effects. The determination of bound steroids will be carried out by means of a DEAE-cellulose filtration assay.

79. MECHANISM OF HORMONE ACTION ON TARGET CELLS IN CULTURE

Sonnenschein, C., Soto, A. M., Lee, H., Ucci, A. A., Tufts University, Boston Campus, School of Medicine, Dept. of Anatomy, *136 Harrison Ave., Boston, Massachusetts,* 02111, United States of America

A study of growth and several other parameters affected by 17-beta-estradiol administration in estrogen (E)-sensitive pituitary and mammary tumor cells in rats of different ages and sexes is proposed. These cells which carry E receptors and grow faster in adult females than in adult males show a similar character when injected into either male or female newborn (NB) rats exclusively. A significant growth delay is seen, however, when these same cells are injected into the NB rats of both sexes. This delay seems to be mediated by the action of alpha-fetoprotein (AFP). No such delay in growth is observed when injected cells are E receptor-carrying cells but autonomous in growth (they grow at the same speed regardless of whether they are injected into males or into females). The further characterization of this delayed period of growth will be done using rat pituitary and rat mammary tumor cell culture systems that are a) E sensitive or b) autonomous. AFP will be purified by biochemical methods (gel electrophoresis, chromatography) and its effect on E target cells will be tested in the cell culture system. E and thyroid hormones will be tested for their ability to affect the growth of these target cells under a variety of conditions in animals and in cell culture. A mechanism similar to that probably responsible for the inhibition of growth of E-sensitive tumor cells should be active as well in the development of normal E2 sensitive target cells such as vagina and uterus cells. This inference is drawn based on the results of experiments described. The study of the mechanism of sex steroid action in adult rats is also proposed.

80. ROLE OF ESTROGEN RECEPTORS IN HORMONAL CONTROL OF GROWTH

Jensen, E. V., University of Chicago, Pritzker School of Medicine, Dept. of Biophysics & Theoretical Biology, *5801 S. Ellis Ave., Chicago, Illinois,* 60637, United States of America

Association with estradiol renders the extranuclear receptor protein (estrophilin) of rat or calf uterus susceptible to temperature-dependent conversion to a new form that can be recognized by an increased sedimentation coefficient and by the ability of this 'transformed' or 'activated' hormone receptor complex to bind to uterine nuclei and to enhance their RNA polymerase activity. Because the effect on RNA synthesis is specific for hormone-dependent tissues and is similar both in magnitude and in effect on RNA composition to that observed in rat uterine nuclei after estrogen is given in vivo, the nature of the apparent deficiency in the uterine polymerase system and its alleviation by transformed complex merit detailed study. Aspects now being investigated include: (1) attempts to stimulate polymerase II in addition to polymerase I in isolated uterine nuclei; (2) identification of the stimulatory effect with an action on chromatin, on the polymerase enzyme, or both; (3) studies of the interaction of transformed complex with purified polymerase enzyme systems; and (4) determination of the biological activity of the uncomplexed estrophilin, now that the transformed receptor protein can be obtained free of steroid. The results will be correlated with those from other studies involving the molecular nature of the transformation phenomenon and the isolation and analysis of native and transformed estrophilin. The action of the purified estradiol receptor complexes on the RNA polymerase activity of uterine nuclei will be determined.

81. HORMONAL REGULATION OF CULTURED ENDOMETRIAL CELLS

Gerschenson, L. E., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Pathology, *4200 E. 9th Ave., Denver, Colorado,* 80262, United States of America

A technique to culture epithelial rabbit endometrial cells in chemically defined medium has been developed. Estrogens were found to promote cell division, while progesterone had an opposite effect. These cultured cells were found to be either noncycling (G0) or cycling. Both cell subpopulations were isolated and it was found that the G0 cells were the target of estrogens. Interaction between progesterone and the cycling cells was necessary to obtain an antagonistic effect on the estrogen action on the G0 cells, apparently due to the production of a diffusible factor. A similar factor, probably a protein, appears to be produced by high density cultures, which do not respond to estrogen stimulation.

Estradiol and progesterone decrease the number of estrogen receptors in cultures, apparently by different mechanisms of action. We will continue to study our experimental system by analyzing the mechanism of action of ovarian sex hormones, epidermal growth factor and prostaglandin F-2alpha in regulating proliferation, cell cycle, blastokinin synthesis, and hormone receptors. The endpoint of our research is to improve our comprehension of the mechanism by which sex hormones regulate proliferation and differentiation of endometrium. It is expected that the study of our hormone-responsive system will help to advance the understanding of the etiology and pathogenesis of endometrial carcinoma in particular and hormone-related cancer in general.

BIBLIOGRAPHIC REFERENCES: J.T. Murai, R.C. Lieberman, J. Yang and L.E. Gerschenson. Decrease of Estrogen Receptors Induced by 17 Beta-Estradiol and Progesterone in Cultured Rabbit Endometrial Cells. Endocr. Res. Comm. 6 (1980) in press. J.T. Murai, C.J. Conti, I. Gimenez-Conti, J.R. Depaoli, E.A. Conner and L.E. Gerschenson. Hormonal Regulation of Proliferation and Differentiation of Rabbit Uterine Epithelium: Cell Culture and Animal Studies. In: The Endometrium, K. Kirton and F. Kimball (Eds.). SP Medical and Scientific Books, Jamaica, N.Y. (1980) in press.

82. HORMONE RECEPTORS IN 3-METHYLCHOLANTHRENE-INDUCED ENDOMETRIAL CARCINOMA

Mortel, R., Pennsylvania State University, Milton S. Hershey Medical Center, School of Medicine, Dept. of Microbiology & Cell Biology, *500 University Dr., Hershey, Pennsylvania,* 17033, United States of America

This is part of a broader project. A summary of this subproject is not available.

83. STEROID HORMONE RECEPTORS IN NORMAL AND MALIGNANT UTERUS (CHICKENS, RABBITS)

Sherman, M. R., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

84. ESTROGEN AND PROGESTERONE RECEPTORS IN DECIDUOMA

Leavitt, W. W., Reuter, L. A., Chen, T. J., Evans, R. W., Muto, M. G., Tetreault, J., Sanford, J., Worcester Foundation for Experimental Biology Inc., *222 Maple Ave., Shrewsbury, Massachusetts,* 01545, United States of America

The decidualized hamster uterus will be used as an experimental model system. Preliminary results indicate estrogen receptor regulation and function may be impaired in deciduoma as compared to myometrium. Studies are designed to: (1) Determine serum steroid (estrogen and progesterone)-receptor (estrogen receptor and progesterone receptor) relationships during decidualization; (2) evaluate the physicochemical properties of cytosol and nuclear receptors; (3) develop a nuclear acceptor site assay to monitor changes that may occur in deciduomal nuclei; (4) establish conditions for culturing deciduomal cells in vitro so as to evaluate effects of steroids, cyclic nucleotides, prostaglandins, and other factors on cell growth and development; (5) identify specific biochemical endpoints of progesterone action in deciduomal cells, including specific proteins, RNA and

DNA synthesis, ornithine decarboxylase, polyamines, cyclic nucleotides, and prostaglandins. These studies will provide information relevant to: a) The treatment of hormone-dependent tumors, and b) the development of new contraceptive techniques.

B. ROLE OF VIRUSES IN GYNECOLOGICAL CANCERS

1. RELATIONSHIP OF HERPESVIRUSES TO GYNECOLOGICAL CANCERS

85. CASE-CONTROL STUDY ON SEXUAL HISTORY OF HUSBANDS OF WOMEN WITH ABNORMAL CERVICAL CYTOLOGY

Buckley, J. D., Doll, R., Harris, R. W., Vessey, M. P., Williams, P. T., University of Oxford, Dept. of Social & Community Medicine, *S. Parks Rd., Oxford OX2 6HE, England, United Kingdom*

If a venereally transmitted agent, such as herpes simplex type 2 virus, induces malignant transformation in the cervix uteri, it would be anticipated that the husbands of women with abnormal cervical cytology would have had more sexual partners than husbands of control women. This would be particularly relevant to women who had had sexual intercourse with their husbands exclusively. In this study, the husbands of approximately 50 single-partner women with abnormal cytology (including invasive carcinoma) and 50 control husbands will be interviewed, and their sexual experience compared. The antibody titres to herpes type 2 will be measured. The first part of the study involving interviews with the women was completed over a year ago and the interviews of their husbands will be presented as a totally unrelated 'health survey.'

86. CASE-CONTROL STUDY ON THE ASSOCIATION OF HERPESVIRUS WITH CERVICAL CANCER IN HUNGARY

Pacsa, A. S., Kummerlaender, L., Pejtsik, B., Pecsi Orvostudomanyi Egyetem, Microbiology Inst.; Virus Laboratory, *Szigeti Utca 12, 7643 Pecs, Hungary*

The project aims to establish herpes simplex virus-specific and cytomegalovirus-specific antigen positivity in cervical cells of women with and without cervical dysplasia. Selected antigen negative and positive cases will be followed up for years registering incidence of dysplasias and tumours in both groups. By this prospective study it is intended to identify whether anaplastic changes of the cervix uteri originate from antigen-carrying cells or not. Cervical imprints and biopsy samples are taken and coded at the Department of Oncology before sending them to the Virus Laboratory for detection of viral antigens by indirect immunofluorescence technique. It is estimated that a total of 1,000 women will be followed up.

87. SEROEPIDEMIOLOGICAL STUDIES OF HERPES VIRUS TYPE-2 AND CARCINOMA OF THE CERVIX IN ISRAEL

Leventon Kriss, S., Menczer, J., Modan, M., Gerichter, C. B., Ministry of Health, Central Virus Lab., *P.O. Box 8255, Tel Aviv, Israel*

The relationship between genital herpetic infection and squamous cell carcinoma of the uterine cervix has been substantiated by sero-epidemiological studies and by evidence of virus persistence in cervical tumor cells. Most studies proving the association between cervical carcinoma and HSV-2 were done in populations with high risk rates for this malignancy. Jewish women are at low risk for this disease. It was, therefore, considered interesting to compare the Jewish population studies with those in other demographic groups, namely Christians and Muslims in Israel.

88. HERPES TYPE 2 VIRUS AND CARCINOMA OF THE CERVIX IN NIGERIANS

Adelusi, B., Osunkoya, B. O., Fabiyi, A., University of Ibadan, School of Medicine, Dept. of Obstetrics & Gynecology, *Queen Elizabeth II Rd., c/o Univ. College Hosp., Ibadan, Nigeria*

Previous serological studies in Ibadan have shown an association between the incidence of type 2 virus and carcinoma of the cervix. Further studies were undertaken to explore the role of the virus, if any, in the genesis of the malignancy by demonstrating the presence of the virus antigen in cervical smears from carcinoma of the cervix patients and its absence in smears from healthy controls, using various immunological methods. The patients were chosen from among those at the Dept. of Obstetrics and Gynecology, U.C.H., while the controls were chosen from among patients attending the family planning clinics of the hospital. Desquamated cervical cells from carcinoma patients and healthy controls were tested for the presence of viral antigens, by the direct immunofluorescence method, using FITC conjugated rabbit antiserum against herpes type 2 virus, and by the indirect immunofluorescence method, using human serum and FITC conjugated rabbit anti-human globulin. Studies are continuing, and biopsy samples from carcinoma of the cervix patients as well as from healthy controls are being collected. The samples are homogenized, and the homogenates are used as antigens for immunization of rabbits. The antibodies so produced are tested against various known antigens, both viral and non-viral, to determine the types of antigens that are present in the cervical biopsy specimens.

89. CERVICAL CANCER IN YUGOSLAVIA

Kessler, I. I., Berger, K., Kulcar, Z., University of Maryland, Baltimore Professional Schools, School of Medicine, Dept. of Epidemiology & Preventive Medicine, *655 W. Baltimore St., Baltimore, Maryland,* 21201, United States of America

Evidence has accumulated suggesting that prior infection with genital herpesviruses may increase risk of developing cervical cancer. This hypothesis was tested by a case-control study in Yugoslavia. (A companion study involving comparisons between 104 carcinoma in situ patients and controls is nearing completion.) An equal number of controls matching the cases in age and nationality were selected. The women were questioned intensively on their sexual, marital and pregnancy histories. In addition, illnesses and hospitalizations were reviewed and a complete gynecological examination including colposcopy was conducted, with two aliquots of blood taken for virological studies. The presence of antibodies to genital herpesviruses was then determined by means of a microneutralization procedure. Analysis continues.

90. HERPESVIRUSES AND CERVICAL CANCER

Rawls, W. E., Clark, A., McMaster University, Dept. of Pathology, *1200 Main St. W., Hamilton, Ontario,* L8S 4L8, Canada

OBJECTIVE: The purpose of the study is to evaluate the role of herpes simplex virus type 2 (HSV-2) in the genesis of cervical carcinoma.

APPROACH: Previous seroepidemiologic studies have demonstrated an excess of antibody activity to HSV-2 among women with cervical carcinoma when compared to control women. However, the degree of association between antibodies to the virus and cervical cancer varies in different populations studied. To better define the meaning of the association, a radioimmunoassay for HSV-2 type-specific antibodies will be used to analyze sera from a series of women with carcinoma of the cervix and from control women.

PROGRESS: A series of about 450 serum samples have been collected from women with cervical cancer and control women. Analyses of the samples for antibody activity to HSV-1 and HSV-2 are under way.

91. SEROEPIDEMIOLOGICAL STUDY OF HERPES SIMPLEX VIRUS IN CARCINOGENESIS OF THE CERVIX

Stern, E., Mickey, M. Y., Takasugi, M., Terasaki, P., University of California, Los Angeles Campus, School of Public Health, Dept. of Public Health, *405 Hilgard Ave., Los Angeles, California,* 90024, United States of America

It is proposed to investigate by a longitudinal study a possible relationship between herpes simplex viruses (HSV), the development of cervical dysplasia, and its progression to cervical cancer. One of the critical issues is the timing of herpes infection in relation to onset of the neoplastic process and a feature of the proposed research is the serial observation and testing of patients to clarify the temporal relationship of herpes infection and carcinogenesis. In considering a longitudinal approach, the relatively low incidence of cervical cancer and the long latency present serious problems of sample size and duration of follow-up. The number of women in the study as well as duration of follow-up can be reduced by following a defined population of women who already have the cancer precursor, dysplasia of the cervix. We have been investigating the possible relationship of steroid contraceptives and carcinogenesis of the cervix by means of a long-term prospective study of women with dysplasia of the cervix. The proposed study on the role of HSV in carcinogenesis of the cervix uses this resource of clinical and laboratory data. Sera already collected from these patients will be used for serial viral antibody studies. Further follow-up of patients and collection of samples will continue.

92. EPIDEMIOLOGY OF CERVICAL CANCER - CHLAMYDIAE AND HERPES

Schachter, J., Hill, E. C., King, E. B., University of California, San Francisco Campus, George W. Hooper Foundation, *551 Parnassus Ave., San Francisco, California*, 94122, United States of America

The goal of this project is to determine whether any of the infectious agents under study are specifically associated with cervical cancer or dysplasia. Prevalence rates will be determined for infection with chlamydiae (debsoniae) - particularly trachoma-inclusion conjunctivitis (TRIC) agents and herpesvirus hominis (HVH) in the cervixes of women examined at the University of California, San Francisco. Those included in these studies will be normal women (routine examination and birth control advice), women being seen for genital tract inflammatory disorders (such as cervicitis and vaginitis), women being examined at the dysplasia clinic, and women who have once had cervical cancer. Isolation attempts will be made, with cervical scrapings taken at the same time as Papanicolaou smears. Serological studies will also be carried out in an effort to obtain evidence of any prior infection with herpes and TRIC agents. Rates of serological positivity for HVH-2 and TRIC agents will be directly compared for women with cervical cancer or dysplasia. Serological results will also be compared for patients with cervical cancer or dysplasia and for normal controls. These controls will be matched with patients by age, race, and several measures of sexual experience. In addition the various indices of sexual experience in patients with dysplasia or cervical cancer and in the controls will be compared.

93. RELATIONSHIP BETWEEN HERPES VIRUSES AND CERTAIN HUMAN MALIGNANCIES

Giraldo, G., Beth, E., Levine, D., Mike, V., Geser, A., Chernesky, M. A., Huraux, J. M., Claudio, F., Giordano, G., Ngu, V., Kyalwazi, S. K., Gharbi, R. M., Memorial Sloan Kettering Cancer Center, Immuno Virology Section, *1275 York Ave., New York, New York*, 10021, United States of America

There is increasing evidence that herpes viruses play a role in the induction of some human cancers (e.g., EBV and Burkitt's lymphoma; nasopharyngeal carcinoma; HSV-2 and cervical cancer; CMV and Kaposi's sarcoma). The main objectives of the project are: (1) To establish an association between the above-mentioned viruses and malignancies by seroepidemiological studies in high and low risk populations; (2) to analyze whether susceptibility to skin cancer can be shown by immunogenetic studies (HLA and MLC) in a high risk population, Tunisian xeroderma pigmentosum patients; (3) field studies in high incidence areas of Kaposi's sarcoma to detect time-space clusters; (4) retrospective analyses of Kaposi's sarcoma patients to determine if Kaposi's sarcoma is more often associated with a second primary cancer than other cancers. Seroepidemiological studies establish the antibody profile against early and late antigens for herpes viruses in cancer patients and controls. Kaposi's sarcoma cases derive from Uganda, Cameroon, Tunisia, France, USA and Italy; skin cancer from xeroderma pigmentosum patients in Tunisia; penile carcinoma from Uganda. Two sex-matched and age-matched (plus or minus 2-5 years) healthy subjects, living in the same areas and in similar socioeconomic conditions, will be used as controls. A second control group will consist of serum samples from age- and sex-matched patients with a cancer of different origin and location but similar therapy.

94. PROSPECTIVE STUDY OF PATIENTS WITH GENITAL TYPE II HERPESVIRUS INFECTIONS

Kaufman, R. H., Adam, I., Baylor College of Medicine, School of Medicine, Dept. of Obstetrics & Gynecology, *1200 Moursund Ave., Houston, Texas*, 77025, United States of America

Women with virologically proven genital herpes are being followed prospectively with regard to the possible development of cervical atypia. Comprehensive epidemiological data are also being collected on these individuals.

95. REGISTRATION OF WOMEN WITH PRIMARY AND SECONDARY GENITAL HERPES SIMPLEX VIRUS (HSV) INFECTION

Vestergaard, B. F., Kobenhavns Universitet, Inst. of Medical Microbiology, Dept. of Clinical Virology, *22 Juliane Mariesvej, DK2100 Copenhagen OE, Denmark*

Recent observations indicate that women suffering from primary genital HSV type 2 infection represent a high risk group for later development of carcinoma of the uterine cervix. The development of a simple, sensitive and reliable enzyme-linked immuno-specific assay (ELISA) for the exact titration of herpes simplex virus type 1 and type 2 specific antibodies in human sera has made it possible to perform serological HSV type-specific diagnosis of clinical cases of genital HSV infections and identify four categories of patients: (1) Primary genital herpes caused by HSV type 2 (HSV infection in an individual who has never had HSV infection before); (2) primary genital herpes caused by HSV type 1; (3) secondary genital herpes caused by HSV type 2 (genital HSV in an individual who has previously had HSV type 1 infection); (4) wrong clinical diagnosis (i.e., the serological result indicates that the patient did not have an HSV infection). It is planned, in a period of three years, to diagnose and register as many of the genital HSV infections as possible - hopefully at least 50% of all cases in Denmark seeking medical care. The later follow-up of the registered cases of genital HSV infection will be performed under the screening programs for cervical carcinoma presently being developed in Denmark. The objective of the study is, by a large-scale prospective investigation, to obtain valid information about: (1) The incidence of genital HSV infection in Denmark and the distribution of primary and secondary cases, and (2) the risk of later development of carcinoma of the uterine cervix.

96. PROSPECTIVE AND RETROSPECTIVE STUDY OF THE POSSIBLE RELATIONSHIP BETWEEN HERPESVIRUS TYPE II INFECTION AND GENITAL CANCER

Naib, Z. M., Nahmias, A., Grady Memorial Hospital, Dept. of Cytopathology, *80 Butler St. S.E., Atlanta, Georgia*, 30303, United States of America

Since 1964, more than 1,500 women were detected during routine cytological screening as having herpesvirus infection. These individuals are followed clinically and cytologically in a special herpes clinic: the incidence of cervical cancer was found to be approximately 10 times higher than in general populations cytologically screened. The main objectives of this study are to investigate the degree of this association and explain the nature of the association and related factors. The incidence of anaplasia was found to be higher in patients with primary herpesvirus type II infection.

97. MALE ROLE IN CERVICAL CANCER

Kessler, I. I., Hebel, J. R., Mabuchi, K., Lin, R. S., University of Maryland, Baltimore Professional Schools, School of Medicine, Dept. of Social & Preventive Medicine, *655 W. Baltimore St., Baltimore, Maryland*, 21201, United States of America

Funds are requested to renew our ongoing study on the role of the male sex partner in the etiology of cervical cancer. The considerable evidence for the relationship between cervical cancer and venereally transmitted genital herpesvirus HSV-2 has been augmented by preliminary findings from this study which are strongly suggestive of a significant male role in cervical carcinogenesis.

Our prospective study is designed to test the venereal hypothesis in cervical cancer pathogenesis. We are seeking a scientifically valid answer to the following question: Is the risk of developing cervical cancer increased in the current wives of men who - at some other time -were married to other women who developed this disease?

Over the past 25 years we have identified nearly 4,200 women with histopathologically confirmed cervical cancer. The husbands of these women are being followed up for the purpose of identifying all their previous and subsequent wives who in turn are traced prospectively through time. The lifetime risk of cervical cancers of these 'case' wives is then compared with that of a cohort of demographically similar 'control' wives. This approach affords an epidemiologically valid test of the role of HSV-2, or any other venereally transmitted male factor, in cervical cancer.

At present, marital clusters of cervical cancer have been confirmed in both wives of each of 45 men, with somewhat more than 1000 husbands and 'other wives' to be traced.

Our work was substantially disrupted by the transfer from Johns Hopkins to the University of Maryland. Funds are requested to complete this unique project.

98. HERPESVIRUS INFECTIONS IN HIGH RISK CANCER GROUPS

Reynolds, D. W., Alford, C. A., Pass, R., University of Alabama in Birmingham, School of Medicine, Dept. of Pediatrics, *1919 7th Ave. S. Birmingham, Alabama*, 35233, United States of America

This project involves study of the natural history of herpesvirus infections in renal transplant patients and low income urban females, two target populations with increased risk of cancer. In renal transplant patients the natural history of cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), and varicella zoster virus (VZV) infections will be investigated. In the low income young women, the natural history of genital HSV and CMV infections will be studied. In both of these populations, particular attention will be payed to factors which lead to reactivation of apparently latent infections. In renal transplant patients the effect of immunosuppression and histocompatability on specific humoral and cellular immunity, viral excretion, and development of clinical manifestations of viral infection will be examined. Young women with cervical CMV and HSV excretions will be characterized by frequency of recurrences in relation to age, parity, presence of infection with more than one viral agent, and cervical cytology.

In both the renal transplant patients and in the normal low income women, an attempt will be made to correlate natural history of viral infections with development of malignancies, should any occur. Children born with congenital CMV who are born to young women in this study will also be compared to uninfected controls with regard to incidence of malignancy. In the case of transplant patients and young women the majority of subjects are expected to be infected with more than one herpesvirus; thus it is unlikely that any etiologic association between malignancy and viral infection can be established through epidemiologic study.

BIBLIOGRAPHIC REFERENCES: Pass, R.F., Whitley, R.J., Diethelm, A.G., Whelchel, J.D., Reynolds, D.W. and Alford, C.A.: Outcome of renal transplantation in patients with primary cytomagalovirus infection. Transplant. Proc., 1979, in press. Pass, R.F., Whitley, R.J., Whelchel, J.D., Diethelm, A.G., Reynolds, D.W. and Alford, C.A.: Identification of renal transplant patients with increased risk of postoperative herpes simplex virus infection. J. Infect. Dis., 1979, in press.

99. FACTORS AFFECTING PREVALENCE OF HERPESVIRUS TYPE II

Stavraky, K. M., Donner, A., Rawls, W., Chiavetta, J., University of Western Ontario, Dept. of Epidemiology & Preventive Medicine, *1151 Richmond St., London, Ontario*, N6A 3K7, Canada

The purpose of this study is to determine the relationship between specific patterns of sexual behavior and the prevalence of antibodies to herpesvirus type II, and to determine whether these patterns vary by social class. The study will be useful in determining the sexual and socioeconomic risk factors for herpesvirus type II infection; this information will in turn assist in directing preventive measures to the highest risk groups. Prevention of infection is worthwhile because there is evidence that herpesvirus type II not only causes a number of usually minor illnesses, particularly genital herpes, but also produces congenital malformations and neonatal disease in the offspring of infected women, and because this virus may be etiologically related to cervical cancer.

The study design is a cross-sectional survey of a sample of English-speaking men and women between the ages of 35 and 50, residing in Metropolitan Toronto. Information on specific sexual behavior, use of contraceptives and demographic attributes will be ascertained by interview and blood samples will be drawn for radioimmunoassay determination of antibodies to herpesvirus type II. A feasibility study of Toronto has demonstrated that a high proportion (90%) of eligible subjects respond favorably to the questionnaire and cooperate with the request for a blood sample.

100. HERPESVIRUS TYPE-2-SPECIFIC ANTIBODIES IN CERVICAL CANCER CASE-CONTROL STUDIES

Dreesman, G. R., Adam, E., Kaufman, R. H., Melnick, J. L., Baylor College of Medicine, School of Medicine, Dept. of Virology & Epidemiology, *1200 Moursund Ave., Houston, Texas*, 77025, United States of America

It has been more than 10 years since herpes simplex virus type 2 (HSV2) was first associated with human cervical carcinoma by seroepidemiological studies. However, the methodology available for these studies produced equivocal results because of the major antigenic cross-reaction expressed between HSV1 and HSV2. Recently, our laboratory developed a micro solid phase radioimmunometric assay (micro-SPRIA) which allows for testing of human sera for type-specific HSV antibody utilizing purified HSV type-specific glycoproteins. We propose to utilize this assay to screen a well-documented case-control bank of sera available in this laboratory. More than 4000 sera are available in the serum bank. The representative antibody status of each patient, as determined by the micro-SPRIA test, will be analyzed to ascertain whether patients with past HSV2 infections have a greater risk of developing cervical cancer than matched controls. Sera from different geographical areas will be studied to determine if HSV2 is the prevalent agent in conjunction with cervical cancer in different populations. Lastly, purified glycoproteins from different HSV2 strains isolated will be studied to determine if possible serological variations between study groups are associated with the origin of the strains.

101. HERPESVIRUS HOMINIS TYPE 2 ANTIBODIES IN RELATION TO THE DEVELOPMENT OF CERVICAL NEOPLASIA

Johnson, L., Maddon, D. L., Easterday, C. L., New England Regional Primate Research Center, *1 Pine Hill Dr., Southborough, Massachusetts*, 01772, United States of America

An assay of herpesvirus hominis type 2 hemagglutinating antibodies is being made in sera of patients, before the onset of disease, during stages of cervical neoplasia and after treatment and compared with sera of controls who did not develop cancer. This prospective study is possible because sera were collected at the Boston Hospital for Women from pregnant and postpartum women during the years 1959-1965 in the Collaborative Study of Cerebral Palsy. These same women had Papanicolaou smears taken during the same time period in a study of the histogenesis of cervical neoplasia. A sample group of the women was re-examined for cervical neoplasia and serum was collected during the years 1974-1977.

102. STUDIES ON THE POSSIBLE VIRAL ETIOLOGY OF HUMAN MALIGNANCIES

Melnick, J. L., Adam, E., Dressman, G., Baylor College of Medicine, School of Medicine, Dept. of Virology & Epidemiology, *1200 Moursund Ave., Houston, Texas*, 77025, United States of America

Serum samples of patients with cervical cancer and matched non-cancer control women are examined for antibody to individual HSV-2 induced antigens. The study attempts to answer the following questions: (1) Is there an increase in the capacity to react with HSV non-structural antigens? (2) What is the significance of finding HSV-induced DNA-binding proteins in biopsy-obtained cells of women with severe dysplasia and carcinoma?

103. HERPES VIRUS CODED INFORMATION IN CELLS DERIVED FROM CERVICAL CARCINOMA, PREMALIGNANT LESIONS OF THE CERVIX AND CELLS TRANSFORMED IN VITRO

Wilkie, N. M., Macnab, J. C., Sharp, F., Clemments, J. B., University of Glasgow, Inst. of Virology, *Church St., Glasgow G11 5JR, Scotland, United Kingdom*

OBJECTIVE: To analyze which (if any) regions of the herpes simplex virus (HSV) genome are expressed in cells obtained from biopsies of cervical malignancy, premalignant dysplasia and carcinoma in situ, and from HSV transformed cells, and to relate this to the known physical maps of HSV coded functions and to other virogenes. The results may help resolve whether herpes viruses (or other viruses) play a role in the development of the disease.

APPROACH: Punch biopsy samples taken from patients with premalignant or malignant disease will be cultured in vitro, used to prepare thin sections and used as a source of nucleic acid extracts. An essential control will be to analyze the tissue for the presence of infectious virus. The cells and tissues will be examined for the presence of HSV coded RNA and DNA, using as probes highly specific HSV DNA obtained by cloning subfractions of the genome in the bacterial plasmid pBR322 (U.K. guidelines, GMAG proposal S607/21/2). The main approaches will be to test for m-RNA in specific cell types using in situ hybridization and to examine the total tissue content of virus coded nucleic acid using hybridization to virus or cell DNA immobilized on nitrocellulose membrane filters. Well characterized HSV-transformed cells will be used to calibrate the sensitivity of the technique. The approach has the potential to determine if specific sub-regions of the genome are being expressed. These can then be compared to the nucleic acid sequences present in a number of other human viruses.

104. PRESENCE OF HERPES SIMPLEX VIRUS INFORMATION IN HSV TRANSFORMED CELLS AND IN BIOPSY SPECIMENS BY IN SITU HYBRIDIZATION

Brown, G., Biswal, N., Levy, C. C., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Molecular Biology Laboratory, *Baltimore, Maryland,* 21201, United States of America

Radiolabeled DNA and its restriction endonuclease fragments are being used in hybridizations to determine which regions of the HSV genome are present in HSV transformed cells and in cervical biopsy specimens from normal donors and those with dysplasia and carcinoma.

105. VIRAL GENES AND GENE PRODUCTS IN HERPES SIMPLEX VIRUS-TRANSFORMED CELLS

Schaffer, P. A., Weller, S. K., Sidney Farber Cancer Center Inc., Dept. of Microbiology & Molecular Genetics, *44 Binney St., Boston, Massachusetts,* 02115, United States of America

The purpose of this investigation is to identify the HSV DNA sequences and gene products in HSV-transformed cells and to isolate and characterize transformation-defective mutants of the hr-t class in an effort to identify essential transforming genes of HSV. The following series of studies is proposed: A series of viral-antigen-positive cell lines transformed in vitro by HSV-1 and -2 antigen-positive cervical carcinoma cell lines will be characterized with regard to the viral DNA sequences which they contain in order to identify the set of DNA sequences common to all lines. Virus specific mRNA will be a) isolated from transformed cells by hybridization to labelled viral DNA fragments and b) translated in vitro in order to identify viral proteins encoded therein. Viral proteins will be identified in transformed cells by immunofluorescence and immunoprecipitation tests using potent antisera to HSV-infected and transformed cells, and to individual viral polypeptides. The map locations of DNA templates specifying proteins found in all or most transformed cell lines will be determined by hybrid-arrested translation of viral mRNA from transformed cells and by the analysis of HSV-1 x HSV-2 recombinants generated in crosses between pairs of HSV-1 and -2 ts mutants available in this laboratory. Intact viral DNA and DNA fragments corresponding to a) the DNA sequences in transformed cells and b) the sequences specifying potential 'transforming' proteins will be mutagenized in vitro and mutations will be rescued by coinfection of susceptible cells with intact wild-type virus DNA. Mutants able to replicate in HSV-transformed cells but not in normal cells (hr or host-range mutants) will be sought. Such mutants may be defective in essential transforming genes and thus, will be tested for their transforming ability. Transformation-defective hr mutants (hr-t mutants) will then be characterized genetically and biochemically in order to elucidate the function of the mutant gene.

106. BIOPHYSICAL PROBES FOR MALIGNANT CELLS

Todd, P. W., Docherty, J. J., Pennsylvania State University, University Park Campus, School of Science, Dept. Microbiology, Cell Biology, Biochemistry & Biophysics, *211 Whitmore Lab., University Park, Pennsylvania,* 16802, United States of America

The presence of herpes simplex virus (HSV) proteins will be developed as a biophysical marker of malignancy and early malignant states in human uterine cervical cells. Since work to date indicates that HSV is associated with uterine cervical carcinoma and that carcinoma cells should contain HSV proteins, we plan to identify those proteins associated with these cancer cells and use them to produce antibodies. We shall detect these proteins using biophysical probes and laser flow cytometry. Previously identified tumor-associated viral antigens will be isolated and purified by preparative electrophoresis, and specific antibodies to them will be prepared in animals and hybridomas. These antibodies will be reacted with uterine cervical cells from normal subjects, patients with HSV infections, patients with dysplasia, and carcinoma patients.

HSV-transformed cultured cells will be used to optimize procedures. The presence of marker proteins will be detected with fluorescently labeled secondary antibodies, fluorescent avidin, or by the peroxidase-antiperoxidase staining method. These fluorescent or absorbing stains will be evaluated by semi-automated quantitative microscopy, laser flow microfluorometry, or laser flow light scattering cytometry in 2-parameter or 3-parameter flow cytometers. The optimum choice of antigen, antibody, biophysical probe, and cytometry system will be made on the basis of an objective comparison of biophysical and clinical findings.

107. HERPESVIRUS ANTIGENS IN TRANSFORMED CELLS

Cabral, G. A., MarcianoCabral, F., Virginia Commonwealth University, School of Basic Sciences & Graduate Studies, Dept. of Microbiology, *901 W. Franklin St., Richmond, Virginia,* 23284, United States of America

Work is in progress to develop continuous cell cultures of cells originating from cervical squamous cell carcinomas. Cells will be examined for the expression of HSV-associated antigens using immunofluorescence, immunoperoxidase, and electron-microscopic procedures. In addition, primary cell cultures and explant outgrowths of cervical fragments originating from individuals with squamous metaplasia, dysplasia and carcinomas in situ will be examined for HSV-associated antigens.

Matching sera will be tested for the presence of antibodies to HSV-1 or HSV-2 using virus neutralization or passive hemagglutination techniques. The presence and titer of antibodies to HSV will be correlated to the stage of cervical disease and to the expression of HSV-associated antigens in cervical biopsy materials and in cultured cells derived from these biopsies.

108. IDENTIFICATION OF CELLULAR GENES WITH TRANSFORMING POTENTIAL

Stephenson, J. R., van de Ven, W. J., Sacks, T. L., Devare, S. G., Deobagkar, D. N., Nalewaik, R. P., Kelloff, G. J., Moldow, C. F., Reynolds, F. H., Hampar, B., Gilden, R. V., Khan, A. S., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Viral Genetics Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

Replication-defective transforming viruses including one isolate of cat, and two of mouse origin have been shown to encode polyproteins containing components corresponding to the amino terminus of type C viral gag gene as well as non-structural components. The possibility that these latter components have transforming potential is indicated by studies of transformation-defective mutants. Polyproteins encoded by such studies have been purified to homogeneity and subjected to detailed immunologic and biochemical analysis. In other studies, intracistronic mapping of the gag regions of the genomes of representative type C and type D retroviruses has been accomplished by use of a combination of genetic and immunologic approaches. High frequency genetic recombination within the env genes of diverse retrovirus isolates is shown to involve sequences that are involved in host cell receptor site recognition and to be a major factor influencing leukemogenicity. In addition, immunoprecipitation assays for structural proteins of herpes simplex viruses 1 and 2 have been developed and collaborative efforts to re-evaluate the possible role of herpes simplex 2 in cervical carcinomas are in progress.

BIBLIOGRAPHIC REFERENCES: Heilman, C.J., Zweig, M., Stephenson, J.R. and Hampar, B.: Isolation of a nucleocapsid polypeptide of herpes simplex virus types 1 and 2 possessing immunologically type-specific and cross-reactive determinants. J. Virol. 29: 34-42, 1979. Devare, S.G. and Stephenson, J.R.: Primate retroviruses: Intracistronic mapping of type D viral gag gene by use of nonconditional replication mutants. J. Virol. 29: 1035-1043, 1979.

109. DETECTION OF HSV-2 RELATED FUNCTIONS IN HUMAN CERVICAL CANCER CELL LINES

Ojeda, J. M., Suarez, M., Cortes, P., Universidad de Chile, Fac. de Medicina, Dept. de Microbiologia y Parasitologia, *Casilla 6539, Santiago, Chile*

OBJECTIVE: Establishment of human cell lines derived from cervical cancer and the investigation of HSV-2 viral functions in these cells.

The new human cell lines (AdGo and DiVa) have been established and characterized in cytological and cytogenetic studies in our laboratory. These cell lines exhibit some HSV-2 related functions such as the presence of Fc receptors detected by immunohemadsorption assay.

The studies are currently focused on the detection of viral structural and nonstructural HSV-2 antigens in both cell lines.

110. RELATION BETWEEN HERPES SIMPLEX VIRUS TYPE 2 INFECTION AND HUMAN CERVICAL CANCER

Walboomers, J. M., van den Berg, F. M., Ree, E., Ketting, B. W., BeckerBloemkolk, M. J., Universiteit van Amsterdam, Lab. for Pathological Anatomy, Experimental Oncology Section, *Eerste Helmersstraat 104, Wilhelmina Gasthuis, Amsterdam, Netherlands*

OBJECTIVE: The main goal of this research project is to identify herpes simplex virus type 2 DNA sequences involved in oncogenic cell transformation and to study their persistence in human cervical carcinoma cells. Additionally, virus specific products of the 'oncogene' region will be identified to investigate their persistence in tumor cells and their immunological response in sera of cervical carcinoma patients during the course of the disease.

APPROACH: Different cell systems will be infected with HSV-2 DNA by using the calcium method to obtain cell lines that are biochemically and/or morphologically transformed. By employing preparative agarose gel electrophoresis, viral DNA fragments will be prepared. Purified fragments will be characterized with respect to their biological and biochemical properties. With the aid of the Southern blotting technique and in situ hybridization, herpes specific DNA and RNA sequences will be detected in morphologically transformed cells and human cervical carcinoma cells. By using a combination of electrophoresis and immunology, detection of viral specific products will be carried out in these cells. Sera from cervical carcinoma patients will be assayed for antibodies against virus specific products originating from the 'oncogene' region. During the course of the disease the levels of these antibodies will be followed.

PROGRESS: Initially, sera of patients with cervical cancer and healthy matched controls were investigated on the presence of HSV-2 neutralizing antibodies by determination of the Index II/I. It also appears that in The Netherlands antibodies against HSV-2 are more frequently present in patients with cervical cancer than in controls. This Index II/I was again determined three years after treatment and revealed that there was no simple correlation between increase of HSV-2 neutralization titres and the course of the disease. A new method for isolation of large amounts of HSV-2 DNA from total lysate of infected cells was developed. This DNA was further characterized by electron microscopy, fragmentation with bacterial restriction enzymes and biochemical transformation capacity and appeared useful for the further analysis of the genetic information of the HSV-genome (Walboomers, J. and Ter Schegget, J., Virology 74, 256-258, 1976). (Text Abridged.)

111. A PROGRAM IN VIRAL ONCOLOGY

Rawls, W. E., Bacchetti, S., Branton, P., Graham, F., Smiley, J., McMaster University, *1200 Main St. W., Hamilton, Ontario*, L8S 4L8, Canada

OBJECTIVE: To determine the mechanism by which viruses induce oncogenic transformation and to examine the role of viruses in human cancers.

APPROACH: Studies of the molecular basis of viral transformation are being undertaken using adenovirus type 5 (Ad5), Rous sarcoma virus (RSV), and herpes simplex virus type 2 (HSV-2). The hypothesis being examined is that viral genetic information is inserted into host cell DNA and the gene products coded for by the integrated viral nucleic acid account for the transformed phenotype. This information will serve as a basis for evaluating the role of viruses in human carcinogenesis.

PROGRESS: The transforming ability of Ad5 has been found to involve the integration and expression of the 14% of the left end of the virus DNA. Two gene functions have been delineated in this region of the genome using host range mutants. Available evidence suggests that one gene (group I mutants) may regulate the production of a protein (58K) which is coded for by a second gene (group II mutants).

RSV has been found to alter the levels of cAMP-dependent protein kinase activity in transformed cells. In addition, differences exist in the phosphorylation of proteins of transformed cells as compared to normal cells. These observations complement the findings of others that the transforming gene product of RSV is a protein kinase. We have generated data suggesting that the transforming gene product of Ad5 also has protein kinase activity.

We have examined the putative role of HSV-2 in cervical cancer using a seroepidemiological approach and conclude that the virus may cause a portion of the cancer cases; this proportion varies from population to population. Initial attempts to evaluate the mechanism of transformation of the HSV-2 at the cellular level suggest, in confirmation of others, that stable integration of the viral DNA may not occur. However, our studies involved biochemical transformation with the thymidine kinase gene and this may not be comparable to oncogenic transformation.

112. ISOLATION AND CHARACTERIZATION OF HOST-RANGE MUTANTS OF HERPES SIMPLEX VIRUS TYPE II AND ADENOVIRUS

Frost, E. H., Institut du Cancer de Montreal, *1560 Est Rue Sherbrooke, Montreal, Quebec*, H2L 4M1, Canada

A special class of mutants of adenovirus (Ad) and polyoma (Py) have been selected for growth in cells transformed by these viruses but not in untransformed cells. These mutants, called hr mutants, are situated in the transformation genes and have lost the ability to cause stable transformation. Due to its relevance to human cervical cancer I would like to isolate similar mutants from HSV-2 and characterize them in the following manner: 1) Locate the mutation: This will provide evidence for the location of the viral transformation sequences. I intend to confirm this by transforming cells with separated restriction endonuclease fragments of DNA. This information will be valuable in directing the search for viral markers (DNA, RNA, proteins) in transformed and cancer cells. 2) Viral growth properties: In order to understand the role of the viral transformation gene in lytic infection I will determine the hr mutant's ability to synthesize viral DNA and, in collaboration with Dr. Martha Suh, viral polypeptides. I will also determine the ability of the mutants to transform cells using DNA fragments to prove that the mutation is in the transformation sequences and not in a regulatory gene. 3) Host range of the mutants: Ad and Py hr mutants grow in some transformed cells but not in others indicating either that the transformation character necessary for hr mutant growth is not expressed in all lines and/or some cell lines are partially resistant to viral growth. These alternatives can be studied in the Ad system where transformation character negative (HeLa) and resistant (Ad transformed 14b) cells exist. I propose to locate the block in resistant cells to distinguish them from those not expressing the necessary transformation character. I will then attempt to overcome this resistance. This knowledge will then be applied to the study of the host range of HSV-2 mutants, particularly their interaction with cervical carcinoma cells which may be transformed and/or rendered resistant by HSV-2. The examination of the growth potential of HSV-2 hr mutants in a number of cell lines, including organ cultures, is proposed to point out specificity or reveal a common transformation character.

113. HERPES VIRUS INDUCTION OF CERVICAL CANCER

Sly, L. D., Meloy Lab. Inc., *6715 Electronic Dr., Springfield, Virginia*, 22151, United States of America

All male Cebus monkeys will be eliminated from the colony during the upcoming contract period. Sixty females which have shown significant cervical anaplasia as a response to inoculation with herpes simplex Type 2 will continue to be kept, as will forty females which have received simultaneous inoculations of herpes simplex Type 2 and various hormone preparations.

2. ROLE OF OTHER VIRUSES IN GYNECOLOGICAL CANCERS

114. ROLE AND SIGNIFICANCE OF HUMAN PAPILLOMA VIRUS INFECTION IN THE GENESIS OF CERVICAL NEOPLASIA

Meisels, A., Hopital du St-Sacrement, Laboratory Medicine, *1050 Chemin Ste-Foy, Quebec, Quebec*, G1S 4L8, Canada

OBJECTIVE: We intend to determine whether human papilloma virus (HPV) infection of the cervix (flat condylomata), a sexually transmitted disease, is morphologically similar to mild and moderate dysplasia, but regresses without any direct relationship to the latter; or whether flat condylomata are really identical to mild and moderate dysplasia, which would indicate that HPV may play a role in the development of cervical neoplasia.

APPROACH: There are precise criteria for differential diagnosis of condylomata of the cervix, based on clinical, cytologic, colposcopic and histopathologic studies. With these criteria it was found that condylomata of the cervix are much more frequent than was formerly suspected. We now intend to specify the differential diagrostic criteria of condylomata using immuno-peroxidase (Pap test), immunofluorescence and immune electron microscopy, using an anti-HPV. Ultrastructural histomorphology of condylomata and mild and moderate dysplasia will be reviewed. We hope to find ultrastructural criteria of differential diagnosis and possibly some evidence on which to base predictions as to which of the intraepithelial lesions are more likely to progress towards invasive neoplasia.

Finally, regression, persistance or progression of condylomata will be studied on an epidemiological basis using our computer files which contain data on more than 250,000 patients of which more than 3,600 exhibit some evidence of intraepithelial lesions of the cervix. When we reviewed these intraepithelial lesions using the new differential diagnostic criteria, it was found that over 70% could be considered condylomata on light microscopic examination. Our epidemiological studies should reveal the evolution of these condylomatous lesions.

It is hoped that this work will help to clarify the significance of human papilloma virus infection as related to cervical neoplasia.

115. THE ASSOCIATION OF CYTOMEGALOVIRUS WITH HUMAN MALIGNANCIES

Norval, M., Hart, H., Neill, W., University of Edinburgh, School of Medicine, Dept. of Bacteriology, *Teviot Pl., Edinburgh EH8 9AG, Scotland, United Kingdom*

OBJECTIVE: Primarily we wish to determine whether cytomegalovirus is involved as an aetiological agent in cancer of the cervix, prostate and colon in man. In addition, we wish to ascertain the association of this virus with human cells in vitro, such as in transformation and persistence.

APPROACH: We will survey patients with malignancies of the colon, prostate and cervix for the presence of cytomegalovirus, utilizing methods to detect virus, viral antigens, antibodies and nucleic acids. Also, we will study the association of cytomegalovirus with human cells, in particular whether it is capable of transformation and whether it can replicate in mononuclear cells.

116. VIRAL PARTICLES AND CYTOGENETICS IN CANCER OF THE UTERINE CERVIX

Iwakawa Shiga, L., Centro de Microscopia Electronica, Instituto del Cancer, *Casilla de Correo Central 781, 5000 Cordoba, Argentina*

We are undertaking the morphologic study of viral particles using the electron microscope. This involves karyotyping of cancerous uterine cells using the 'squash' technique and ultrastructural study of cellular organoids in carcinoma of the uterine cervix. (Translated)

117. VIRUS ASSOCIATED ANTIGENS IN GYNECOLOGIC CANCERS (HUMAN)

Lewis, J. L., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

118. OVARIAN CANCER AND VIRUSES

Stematsky, G. T., Menczer, J., Modan, M., Ministry of Health, Central Virus Lab., *P.O. Box 8255, Tel Aviv, Israel*

Case-control studies have indicated past subclinical infection with mumps virus of groups of ovarian cancer patients and the affinity of the mumps virus to the ovary has been demonstrated. An attempt to grow ovarian cancer tissue as well as virus will be made. Serological studies of antibodies to various viruses will also be undertaken in cases and controls.

119. CULTURE AND TRANSFORMATION OF RAT OVARIAN CELLS

Auersperg, N., Adams, A. T., University of British Columbia, Dept. of Anatomy, *2075 Wesbrook Pl., Vancouver, British Columbia*, V6T 1W5, Canada

There is no direct experimental evidence for the susceptibility of ovarian cells to oncogenic viruses. This study was undertaken to examine the susceptibility of rat ovarian cells to C-type RNA tumor viuses and, if successful, to establish a model for virally induced ovarian cancer.

Initially, cells from young adult rats were cultured and specific cell types were identified by morphology and histochemical characterization of steroid dehydrogenases. Work is under way to establish methods to grow pure cultures of specific ovarian cell types, with emphasis on surface epithelium. Subsequently, both cultures from whole ovary and cultures of pure cell types will be examined for susceptibility to murine sarcoma viruses, and any transformed lines obtained will be examined, in vivo and in vitro, for resemblance to specific groups of ovarian carcinomas in humans.

C. RADIATION AND CHEMICAL INDUCTION OF EXPERIMENTAL GYNECOLOGICAL CANCERS

120. MEDIUM (LOW) LEVEL LONG-TERM EFFECTS OF RADIATION

Ullrich, R. L., U.S. Dept. of Energy, Oak Ridge National Lab., Biology Div., *P.O. Box X, Oak Ridge, Tennessee*, 37830, United States of America

The purpose of this project is to examine the tumorigenic effects of low dose rate gamma ray exposures in several murine tissues which are sensitive to tumor induction with radiation and whose tumorigenic response to acute gamma rays is well defined. The experiments are comparing the effects of high (40 rad/min) and low (1 rad/day) dose rate gamma ray exposure on the induction of lung adenocarcinomas, mammary adenocarcinomas, and ovarian tumors in the BALB/c mouse. The lack of adequate information on dose rate effects of low LET radiation remains a serious problem when the risks of environmental radiation exposures are assessed. This is true for the assessment of carcinogenic risks from exposure to low LET radiation and for the assessment of the relative biological effectiveness of high LET radiation. Since similar studies, examining neutron effects using these endpoints, are being conducted in our laboratory, this study will provide information on the low dose rate effects of gamma rays; it will also provide information necessary to evaluate the relative biological effectiveness of neutrons. In addition, such a comparison will provide new information on the relative degree of recovery from carcinogenic injury which can occur after gamma and neutron irradiation.

121. THE EFFECT OF CLOMIPHENE CITRATE ON VAGINAL DIFFERENTIATION IN THE MOUSE

Gorwill, R. H., Steele, H. D., Sarda, I. R., Queen's University, Dept. of Obstetrics & Gynaecology, *King St. W., Kingston, Ontario*, K7L 3N6, Canada

OBJECTIVE: The objective is to assess the effect of clomiphene citrate on developing cervical vaginal epithelium in the mouse.

APPROACH: This is achieved by giving clomiphene citrate at low and high doses to neonatal female mice with subsequent sacrifice over 24 weeks to compare the effects produced on the developing cervical vaginal epithelium in comparison with vehicle-only injected controls and DES injected controls.

122. MECHANISM OF CHEMICALLY INDUCED HEPATOMAS AND OVARIAN TUMORS

Thorgeirsson, S. S., Smith, C. L., Mattison, D. R., Johnson, E. F., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Biochemical Pharmacology Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The long-range purpose of this project is to study the mechanism of chemically induced hepatomas and ovarian tumors. We are particularly interested in the role of environmental contaminants such as the polycyclic hydrocarbons, nitroso-compounds, N-acetylarylamines, as well as antitumor agents, in initiating these tumors, plus the role of genetic predisposition in development of these tumors. These tumors, at various time points during their development, will then be used as models for evaluating chemotherapeutic agents and other drugs which might be of therapeutic value. Topics of present interest are: (1) The role of metabolic activation, as well as the genetic control of activating enzymes, in the chemical initiation of hepatoma and ovarian tumors; (2) the time course of hepatoma and ovarian tumor formation with particular emphasis on the changing enzyme patterns as the cells become increasingly dedifferentiated; (3) isolation and characterization of premalignant cell populations in the liver.

BIBLIOGRAPHIC REFERENCES: Johnson, E.F., Levitt, D.S., Muller-Eberhard, U., and Thorgeirsson, S.S.: Divergent pathways of carcinogen metabolism: Metabolism of 2-acetylaminofluorene by multiple forms of cytochrome P-450. Cancer Res. 1980 (in press). Thorgeirsson, S.S., Levitt, D.S., and Smith, C.L.: Induction of N- and C-Hydroxylations of 2-Acetylaminofluorene in Rat Hyperplastic Liver Nodules and Hepatomas. International Symposium on Microsomes, Drug Oxidation and Chemical Carcinogenesis: Ann Arbor, Michigan, July 15-18, 1980 (in press).

123. CARCINOGEN-INDUCED CHANGES IN STEROID HORMONE ACTION

Rao, B. R., Washington University, School of Medicine, Dept. of Radiology, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

We previously reported that 7,12-dimethylbenz(a)anthracene (DMBA) competes with progesterone for progesterone serum carrier protein(s) and target tissue receptors. In addition, we established that DMBA is a mild progestational agent. DMBA administration increases the uterine weight and induces endometrial glandular differentiation in estrogen primed rabbit. Additionally, DMBA treatment reduced uterine estrogen receptor level to below the detectable level on day 20 and there was a three-fold increase in progesterone receptor level. DMBA injected into mammary pads of rats and rabbits induced hyperplasia in stromal cells following 10 days of treatment and increased the progesterone receptor levels, while there was no change in estrogen receptor levels. Attempts to separate those hyperplastic cells from other mammary cells based on size and density using albumin gradient centrifugation was not successful. In order to detect whether estrogen receptors are present in those hyperplastic cells induced by DMBA, a specific fluorescent probe was developed by conjugating fluorescein to estrogen. We are now able to detect cells containing estrogen receptors using the fluorescein conjugated estrogen and will use this technique to detect cells containing estrogen receptors. We plan to use a similar fluorescent probe to detect progesterone receptors. The fluorescent probe technique may provide a means to detect those cells in which there is either an increase or decrease in estrogen and progesterone receptors.

II. EPIDEMIOLOGY OF GYNECOLOGICAL CANCERS

A. EPIDEMIOLOGICAL STUDIES OF CERVICAL CANCER

124. INVASIVE CERVICAL CANCER IN GENEVA

Raymond, L., Obradovic, M., Registre Genevois des Tumeurs, Centre de Cytologie et de Depistage du Cancer, *55 Blv. de la Cluse, 1205 Geneva, Switzerland*

This investigation is a restrospective study of the frequency and chronological distribution of cytological examinations of cervical smears in women who developed invasive cervical cancer between 1970 and 1975. Cases are compared with controls, i.e., screened women who did not develop invasve cervical carcinoma, matched by age, vital data and nationality. The results of the study will help to determine the optimal interval between successive screenings.

125. GEOGRAPHICAL DISTRIBUTION, SOCIOLOGY AND CLINICAL AND MICROSCOPICAL PICTURE OF CERVIX UTERI CARCINOMA IN STEIERMARK

Pickel, H., Lahousen, M., Goelles, J., Universitat Frauenklinik, Zytologisch Histologisches Lab, *Auenbruggerplatz 14, 8036 Graz, Austria*

Correlation will be sought for patients with cervix uteri carcinoma residing in the Federal Land of Steiermark between place of residence, social status and clinical stage of the tumor. Relations between the above and the frequency and localization of lymph node metastases, histological appearance and frequency of recurrence will be examined.

126. ASPECTS OF CANCER OF THE UTERINE CERVIX IN JAMAICA

Persaud, V., University of the West Indies, Dept. of Anatomical Pathology, *Kingston 7, Jamaica*

The crude incidence of cervix cancer (39.4 per 100,000 per annum) in Jamaica is among the highest in the world. The university departments of pathology, social and preventive medicine and obsterics and gynecology have been undertaking studies on the incidence, aetiology, early detection and morphology of uterine cervix cancer in Jamaica. Incidence figures are obtained from the Jamaica Cancer Registry, Dept. of Pathology, U.W.I., for a well-defined metropolitan population with adequate diagnostic facilities. Early detection by cytology screening in family planning clinics has shown a prevalence of 5.7 per 1,000 women whereas the rate in a low-income, high-risk, general population of 'well' women was 18.0 per 1,000. This discrepancy appeared to be due to the fact that the family planning women were of low parity (para 0-3) and therefore were not at high risk of developing cervix cancer since both groups were matched for age, race and socioeconomic background. A retrospective interview study was carried out on 300 histologically proven cases of cervical carcinoma and 390 'well' controls matched for age, race, and social class. The controls were drawn from a low-income, high-risk general population of women who were cytologically negative for cervix cancer. The questions asked concerned their marital status, number of pregnancies, age at first pregnancy and first coitus, number of coital partners and the circumcision status of these partners and sexual hygiene. The statistically significant factors were grand multiparity, promiscuity, poor sexual hygiene and early age at first coitus and first pregnancy. Studies on the epidemiology and early detection of cervix cancer in Jamaica are still progress.

127. EPIDEMIOLOGY OF CERVICO-UTERINE CARCINOMA AMONG VARIOUS POPULATIONS IN MEXICO

Gaitan Galarza, V., Schulz Contreras, M., Fundacion para el Diagnostico Temprano del Cancer A.C., *Av. Oaxaca No. 96-202, Col. Roma, Mexico City 7, D.F., Mexico*

The objective of this study is to determine the incidence of cancer of the cervix and of benign lesions which could be related to this disease in urban and rural centers, as well as in residential and heavily populated sections of different areas of the country. This study is based on the knowledge that cancer of the cervix is more prevalent in developing countries. In previous studies we have seen that cancer of the cervix is more prevalent in more populated sections of the city.

In several units of F.D.T.C., we are registering each patient that comes in for a Pap smear. In the registry, we record diagnosis of the cervical lesion and the place of origin of the patient, indicating section, rural or semi-urban area.

128. EPIDEMIOLOGY OF PRECANCEROUS AND EARLY NEOPLASTIC LESIONS OF THE UTERINE CERVIX AND CORPUS

Munteanu, S., Institutul Oncologic Cluj-Napoca, Dept. of Early Diagnosis of Uterine Cancer, *34-36 Republicii, 3400 Cluj-Napoca, Romania*

The objective is to examine the relationship between age at first sexual intercourse, age at first birth, marital status, number of births before age 19 and other known aetiological and epidemiological factors and cervical and corpus neoplasia. A form containing 38 groups of questions, all coded, is filled in by any patient attending the Colposcopy Early Diagnosis Clinic, an out-patient clinic in the Oncological Institute. The following investigative methods are used: Physical examination, various cytological and biopsy examinations, colposcopy, and a thorough inquiry into sexual activity. These are repeated periodically. About 2,500 patients with various benign and malignant cervical lesions and 300 patients with endometrial carcinoma have been recorded and are involved in a long-term follow-up study.

129. STUDY OF NUTRITION, STEROID METABOLISM AND THE INCIDENCE OF FEMALE CANCER

Kodama, M., Kodama, T., Aoyama, M. H., Totani, R., Aichi Cancer Center Research Inst., Dept. of Chemotherapy, *81 1159 Kanokoden Tashiro-cho, Chikusa-ku, Nagoya 464, Aichi, Japan*

In various ethnic groups the risk of developing breast cancer is often inversely related to that for cervical cancer. The hormonal environment of the host may somehow be implicated in the induction of these cancers. The relation between the nutritional level, steroid metabolism and the incidence of cervical and breast cancers will be investigated among the inhabitants of urban and rural districts of Japan. The characteristics of patients with such neoplasms will be compared with those of populations with differing cancer risks. The steroid metabolism of each subject will be assessed by estimating the excretions of 14 neutral steroids with 24 hr. urine. Initial results have been published in the Journal of the National Cancer Institute (54:1023-1029, 1975; 54:1275-1282, 1975; 54:41-47, 1977 and 59:49-54, 1977, and 61:35-39, 1978).

130. OPTIMAL NUTRITION FOR JAPANESE TO PREVENT CANCER

Kagawa, Y., Ebihara, A., Hamamoto, T., Jichi Medical School, Dept. of Biochemistry, *3311-1 Yakushiji, Minami, Kawachi-machi, Tochigi-ken 32904, Japan*

Japanese are very different from Caucasians in their incidence of stomach cancer, breast cancer, etc. This may be due to differences in dietary habits, genetic factors, etc. Stomach and uterine cervix cancer are now rapidly decreasing in Japan, perhaps owing to the impact of westernization. However, breast and colon cancer are increasing. Optimal nutritional conditions which will keep death rates as low as possible will be sought by means of medical and ecological surveys carried out in remote parts of Japan where people are long-lived and traditional habits still remain, since there have been dramatic changes in the life styles and dietary habits of Japanese. Statistical data on average Japanese will be used as a control. Nutrition is assessed by the National Survey which annually samples 10,000 randomly selected households for a three-day period. A district in Okinawa is followed closely, as are students of Jichi Medical School, in relation to dietary habits and disease.

131. ANALYSIS OF MASS HEALTH EXAMINATION FOR UTERINE CERVICAL CANCER IN JAPAN

Yanagawa, H., Hashimoto, T., Gotoh, A., Yokoyama, H., Oda, S., Kawaguchi, T., Jichi Medical School, Dept. of Public Health, *3311-1 Yakushiji, Minami, Kawachi-machi, Tochigi-ken 32904, Japan*

The effectiveness of mass health examinations for uterine cervical cancer is being evaluated with the aid of mathematical models based on the standard examination system widely employed in Japan. Epidemiological data such as incidence and prevalence rates of early and later stages, and mortality rates from cervical cancer were collected from 18 local cancer institutions. Evaluation of the mass examination is performed according to the interval between examinations, coverage rate in the population, and selection of high risk populations.

132. EPIDEMIOLOGICAL STUDY OF CARCINOMA OF THE UTERINE CERVIX RELATED TO BATHING HABITS

Dvivedi, M. S., Cancer Hospital, *Indore 452001, Madhya Pradesh, India*

It is an established fact that carcinoma of the uterine cervix is more prevalent in low socioeconomic groups even in developed areas. There is a possibility that low socioeconomic groups do not have proper washing facilities in their dwelling places. It is presumed that women who submerge the pelvis in a bath tub might cleanse the vaginal passages more effectively than those who take a shower. In India it is rare to have a bath tub in the bathroom even in the urban population. The usual method of taking a bath is by a bucket and mug. In the rural areas the source of water is either tanks, rivers or rivulets and either the women bathe at their own house using a bucket and a mug or at these other sources of water. In the present study we are studying habits of patients reporting with carcinoma of the uterine cervix for treatment at this center. We are also studying the bathing habits of the husbands of the patients with particular reference to circumcision, retraction of the prepuce during washing and cleaning smegma. This study has been undertaken with a view to studying the status of genital hygiene of patients with carcinoma of the uterine cervix. The non-circumcised husbands are questioned to determine how often they remove the smegma when taking a bath. The distributional pattern of the patients according to these habits may give some indication of causative factors of this disease.

133. EPIDEMIOLOGICAL ASPECTS OF A CANCER CONTROL PILOT PROJECT

Narayanan, M., Arignar Anna Memorial Cancer Inst., Dept. of Gynaecology, *Railway Rd., Kanchipuram 631501, Tamil Nadu, India*

Within the framework of a program for the early detection of precancerous lesions and early cancer of the uterine cervix, oral cavity, and pharynx, by systematic clinical examination, cytology and biopsy, aetiological and epidemiological studies will be undertaken. The prevalence and incidence of these cancers will also be assessed. Knowledge, attitudes and practices relating to cancer are being examined in relation to a large number of factors including age, sex, religion, occupation, income, etc. Questions are asked about diet, personal habits, reproduction associated factors, etc.

134. EPIDEMIOLOGY OF DYSPLASIA AND CARCINOMA OF THE UTERINE CERVIX

Roy Chowdhury, J., Chakrabarti, R. N., Saha, I., Dutta, H., Sha, S. P., Roy, N. N., Patra, G. H., Das Gupta, P. S., Ghosh, K., Sarkhel, T., Ghosh, A., Sikdar, S., Chittaranjan National Cancer Research Centre, Depts. of Epidemiology/Pathology, *37 S.P. Mukherjee Rd., Calcutta, 700026, West Bengal, India*

Carcinoma of the uterine cervix is the most common form of cancer among Indian women and more prevalent in low socioeconomic groups. It is accepted that a certain percentage of different grades of cervical dysplasia progress to squamous cell carcinoma. The aim of the present study is to establish the prevalence rate of dysplasia and cancer of the uterine cervix in the urban and rural population in West Bengal and correlate the natural histories of these lesions with age, parity, age at first birth, beginning of sexual relations, marital status, number of births and other known etiological and epidemiological factors. Married women in the age-group ranging from 20-70 years attending the Cancer Detection Centers are questioned thoroughly and forms containing 20 groups of questions are filled out by experts. The following investigations are made: general physical examination, systemic examination, gynecological examination, cytological and biopsy specimen examinations (biopsies are taken from the patients with cancer of the cervix and dysplasia whenever possible). Cases of dysplasia are followed up periodically for a minimum period of 5 years.

135. EPIDEMIOLOGICAL CUM-PREVALENCE STUDY OF CARCINOMA OF THE CERVIX IN URBAN, RURAL AND TRIBAL AREAS IN THE INDIAN POPULATION

Shah, C. A., Gujarat Cancer & Research Inst., Dept. of Gynecology, *New Civil Hosp. Campus Asarwa, Ahmedabad 380016, Gujarat, India*

Carcinoma of the cervix uteri is the most common cancer in Indian women. Through several studies in other parts of the world, the relationship of this cancer with low socioeconomic group, early onset of sexual activity and child bearing is well known. These factors are now being studied in a prospective study in urban, rural and tribal areas in the state of Gujarat, India. The clinical examination includes cytological smears and histological confirmation of suspected cancer. In the first part of the study some 30,000 women have been studied.

136. EPIDEMIOLOGY OF CANCER OF THE CERVIX

Rahim, M. A., Ataharuddin, Q., Elahi, M. F., Haque, M. N., Hossain, M. A., Islam, K. M., Kabir, A., Khair, M. A., Khaleque, S. A., Bangladesh Cancer Epidemiology Research Program, Research Coordinating Unit, *49 E. Azimpur Gov. Estate, Dacca 5, Bangladesh*

OBJECTIVE: The characteristics of groups at high risk for cancer of the uterine cervix will be studied with the help of an ad hoc cancer registry of BCERP. Radiotherapy units of Bangladesh will be places of study, and compilation of data, which will be done manually, will be carried out at Bangladesh Cancer Epidemiology Research Program Research Coordinating Unit.

137. HIGH-RISK GROUPS FOR CANCER OF UTERINE CERVIX

Rahim, M. A., Ahmed, Q. A., Elahi, M. F., Hossain, M. A., Islam, K. M., Kabir, A., Khaleque, S. A., Miah, M. N., Sirajoddowla, M., Dacca Medical College Hospital, Dept. of Radiotherapy & Chemotherapy, *49 E. Azimpur Govt. Estate, Dacca 5, Bangladesh*

The characteristics of groups at high risk of developing cancer of the uterine cervix will be studied with the help of the cancer registry of the Bangladesh Cancer Epidemiology Research Program. The study will be carried out in radiotherapy units in Bangladesh and data will be compiled centrally.

138. BANGLADESH CANCER EPIDEMIOLOGY RESEARCH PROGRAM

Rahim, M. A., Ahmed, Q. A., Kabir, A., Elahi, M. F., Hossain, M. A., Islam, K. M., Khair, M. A., Khaleque, S. A., Miah, M. N., Pati, B. P., Sarma, S. K., Haque, M. N., Dacca Medical College Hospital, Dept. of Radiotherapy & Chemotherapy, *49 E. Azimpur Govt. Estate, Dacca 5, Bangladesh*

The aim is to examine the relative frequency of all cancers. Hospitals where radiotherapy facilities are available have been selected for the study. Participation of other hospitals which lack a radiotherapy center is voluntary. Consultants attached to participating hospitals are co-investigators. After interview and examination a clinical report is prepared, one for each patient, in the ad hoc tumor registry of BCERP. The records are collected centrally for compilation and statistical analysis. Three articles have been published and results show that cancer of the larynx, lung and oropharynx is frequent in males, and cancer of the cervix, breast and oral cavity frequent in females.

139. FREQUENCY OF MALIGNANT TUMORS IN PAKISTAN

Zaidi, M. H., Jafarey, N. A., Masood, S. M., Askari, S. A., Siddiqi, M., Ahmed, M., Rehamm, G., Jinnah Postgraduate Medical Centre, Dept. of Radiology, *Karachi 35, Pakistan*

Hospital-based data on the frequency of malignant tumors are collected from six centers in Pakistan: Hyderabad, Bahawalpur, Multan, Lahore, Rawalpindi and Peshawar. All cases of breast, cervix and bone tumors are included, and in the case-control study information is obtained from patients and from non-cancer outpatients matched for age and sex.

140. FREQUENCY OF CANCER OF THE UTERINE CERVIX IN DIVORCED AND WIDOWED WOMEN

Wakefield, J., Sibary, K., Christie Hospital & Holt Radium Inst., Dept. of Social Research, *Wilmslow Rd., Withington, Manchester M20 9BX, England, United Kingdom*

The records of histologically confirmed cancers and computer records of women who have had abnormal smears are being examined. The categories widowed and divorced are not separated on current record forms, and this study attempts by postal questionnaire to distinguish between the two. Preliminary findings, now being checked on a random sample of 1,200 women, suggest that most of the excess morbidity is accounted for by the divorced category.

141. CASE-CONTROL STUDY OF SQUAMOUS CARCINOMA OF THE CERVIX UTERI

Moriarty, M., Herity, B. A., Murphy, J., St. Luke's Hospital, Radiotherapy & Clinical Oncology Centre, *Highfield Rd., Rathgar, Dublin 6, Ireland*

This case-control study will include 100 patients with invasive cervical cancer, 100 with carcinoma in situ and 100 age-matched controls. Questions will be asked about age, parity, socioeconomic group, marital status, age at first coitus, number of coital partners, age at first pregnancy, etc. The diagnosis of carcinoma in situ will be based on a combination of cytology, colposcopy and histology. A histological diagnosis of severe dysplasia will be considered equivalent to carcinoma in situ. Control subjects will have normal cytology and/or colposcopy.

142. STUDY OF EPIDEMIOLOGY, SOCIOLOGY AND GENESIS OF UTERINE CERVICAL CANCER

MacGregor, J. E., Teper, S., University of Aberdeen, *Aberdeen AB9 1AS, Scotland, United Kingdom*

The northeast area of Scotland is an ideal area for epidemiological studies being centred round one main city, Aberdeen. It is possible to identify individual women screened no matter how many cervical smears they have, how many different clinics they attend or how often they move within the area. Already a very high percentage of women in the region have had one or more cervical smears. A fall in the incidence of the disease has occurred and is continuing. A marked fall in mortality rates has occurred. There have been no deaths of women under 35 years of age since 1973 during which time the death rates in England and Wales were rising. Studies continue, with special emphasis on the genesis of this disease in young women.

143. EPIDEMIOLOGY OF CERVICAL DYSPLASIA

Clarke, E. A., Lickrish, G., Ontario Cancer Treatment & Research Foundation, Division of Epidemiology & Statistics, *7 Overlea Blvd., Toronto, Ontario,* M4H 1A8, Canada

The proposed investigation is a case-control study designed to examine the relationship between cigarette smoking and dysplasia of the uterine cervix. Evidence has accumulated linking cigarette smoking and different sites of squamous cell carcinoma, recently including that of carcinoma of the uterine cervix. It is, therefore, possible that exposure to cigarettes may also increase the risk of cervical dysplasia which is a precursor of invasive carcinoma of the cervix. The cases will be 250 consecutive women between the ages of 20 and 59, seen at the Dysplasia Clinic of the Toronto General Hospital. Two controls will be used, the first being a neighborhood control selected for living as close as possible to the case and the second selected from the practice of the physician who referred the case to the Toronto General Hospital for treatment. Each case and control will be interviewed to obtain information on date of birth, education, income, marital status, race, gynecological and obstetrical history, contraceptive practices, sexual history and smoking habits. The analysis will explore differences between cases and controls in their smoking habits after taking appropriate account of such disturbing variables as socioeconomic status, etc.

144. NATURAL HISTORY OF DYSPLASIA OF THE UTERINE CERVIX

Miller, A. B., Thompson, D. W., Jain, M., University of Toronto, *Medical Sciences Bldg., Toronto, Ontario,* M5S 1A8, Canada

In most models of the natural history of squamous carcinoma of the cervix, dysplasia is regarded as the first recognizable pathological process in an orderly progression from normal to malignant epithelium. Since dysplasia does not always become malignant, there is need to clarify the extent to which regression forms part of the natural history of dysplasia. The present study aims at seeking information on the natural history of cytologically identified but untreated dysplasia in comparison with a sample of normal women with smears examined in the same laboratory. An estimated 10,000 women in the case series of moderate or severe dysplasia and 30,000 in the control series will be included. Information is also being sought on the possible association of oral contraceptive use and the risk of progression of dysplasia. Data extraction is currently under progress.

145. NATURAL HISTORY OF CERVICAL CANCER

Green, G. H., Wright, L. H., Nye, E. B., Auckland University, School of Obstetrics & Gynecology, *P.O. Box 2175, Auckland, New Zealand*

The aim is to ascertain whether or not cervical cancer commences in the pre-invasive form and whether or not the discovery of carcinoma in situ by cytology will decrease the rate of mortality from invasive cervical cancer in the population. The study population consists of all cases of in situ cancer diagnosed and treated at National Womens Hospital, Auckland, New Zealand, (about 150 per annum); all cases of invasive cancer (about 50 to 60 per annum) occurring in populations served by the Auckland Hospital Board (approximately 890,000 in 1978), and all cases of in situ and invasive cancer and their district of origin reported to the National Cancer Registry, Department of Health, Wellington. All clinical and sociological data relative to cases occurring in the Auckland Hospital Board area will be correlated and age-standardized incidence and mortality rates, and trends in these will be calculated for all New Zealand cases. A cytology screening index (number of smears per 1,000 population aged 20 years and over) will be used in association with these analyses.

146. NATURAL HISTORY OF CERVICAL CARCINOMA

Dabancens, A., Prado, R., Salas, C. O., Branes, J., Universidad de Chile, Cancer Cytopathol. & Cont. Svc., *1058 Av. Bernardo O'Higgins, Santiago, Chile*

OBJECTIVE: To characterize the preclinical stages of cervical neoplasia.

APPROACH: Clinical and epidemiological data on several groups of patients with different definitive diagnoses are analyzed.

PROGRESS: Following the report of 648 conizations presented at the 7th Latin American Congress of Obstetrics and Gynecology in Quito, 1973, 1000 new cases that clarify morphological criteria and biopathology of these lesions have been studied.

147. EPIDEMIOLOGICAL ASPECTS OF CARCINOMA OF THE CERVIX

Giordano, C., Nogueira de Carvalho, C. R., Okama, M. N., Homen de Melo, M. R., Casanova, R. O., Faculdade de Ciencias Medicas da Santa Casa de Sao Paulo, Dtpo. de Obstetricia e Ginecologia, *Rua Dr. Cesario Mota Junior, N 112, Sao Paulo 01221, Brazil*

The low income female population constitutes the major portion of those attending the clinics of general hospitals in Brazil for screening for cancer of the uterine cervix. This study aims to characterize, in this low revenue population, those that are at 'high risk' for cervical cancer utilizing 18 variables obtained from complete gynecological examination, cervical cytology, colposcopy and biopsy. The preliminary work of collection of the data has been undertaken over the past two years. The data will now be processed by discriminative analysis to determine which of the variables examined could be a contributing factor to cervical cancer.

148. CARCINOMA IN SITU AND DYSPLASIAS OF THE CERVIX IN RELATION TO AGE, PARITY, AND BEGINNING OF SEXUAL RELATIONS (ABBREV)

Masi, C. A., Ellena, A. N., Bertoli, R., Musacchio, R. M., Inst. Nacional Regional de Oncologia, Dept. of Ginecolonia, *Bv. Zavalla 3399, C.C. No. 366, 3000 Santa Fe, Argentina*

OBJECTIVE: To determine in the healthy cases seen at the Department of Gynecology the incidence of ages of carcinoma in situ and dysplasia for comparison with findings of investigators from other places. The sample group will consist of all healthy patients seen, taking from the registry the data concerning average age of each pathology. At the beginning of this study, we only considered the age; in the last months, we added parity and initiation of sexual relations as other parameters.

149. A PROSPECTIVE SURVEY OF CANCER IN LESOTHO 1970-1974

Martin, P. M., Keen, P., University of Botswana, Lesotho & Swaziland, *Swaziland Campus, Kwaluseni, Swaziland*

One thousand two hundred twenty-three cases of cancer have been collected between 1970 and 1974. The crude rates and epidemiology of the main cancers (cervix, breast and liver) have been determined with the help of the recently published Lesotho Census of 1976. Analysis of the questionnaires completed by the patients shows that they are more traditional, less educated and poorer than a similar group of healthy controls. Furthermore, cervix cancer patients ingest substantially more fermented porridges and drinks which have been recently shown to contain the mycotoxin zearalenone. A recent publication appeared in S. Afr. J. Sci. 75, 501-511, 1979.

150. CERVICAL CANCER EPIDEMIOLOGY IN PANAMA

Reeves, W. C., de Britton, R. C., Benenson, A. S., Joplin, C., Gorgas Memorial Inst. of Tropical & Preventive Medicine Inc., Dept. of Virology, *2007 I St. N.W., Washington, District of Columbia,* 20006, United States of America

In this application we propose to evaluate an unusually high uterine cervical cancer incidence in the Republic of Panama. Panama not only has one of the highest reported cervical cancer rates in the world but also demonstrates marked geographic clustering and a shift in age specific incidence to women in the age group ranging from 20-39 years.

We plan to evaluate this by first recording all cervical cancer cases which occurred between 1974-1978 in a standardized national cancer register. We will then do a seroepidemiologic case-control study comparing socioeconomic, sexual and herpes group virus risk factors which operate in cases and controls. In addition we plan to measure other variables which might account for the unique aspects of cervical cancer seen in Panama. Lastly we will evaluate the effects of the existing Pap smear program and collaborate in initiation of a more intensive screening program.

151. SOCIAL EPIDEMIOLOGY AND CONTROL OF CANCER

Graham, S., Marshall, J., Mirand, E., Greenwald, P., Gentry, J., Mettlin, C., State University of New York, Health Science Center at Buffalo, School of Medicine, Depts. of Sociology/Social & Preventive Medicine, *3435 Main St., Buffalo, New York,* 14214, United States of America

We request renewal of support of this program of research in Social Epidemiology and Control of Cancer. In the area of epidemiology, we would complete analyses on data already collected in the following areas: dietary vitamins, meats, fiber, cruciferous vegetables and other aspects of diet in cancer of the esophagus and larynx, to be studied in cases and controls from Roswell Park Memorial Institute (RPMI); reliability of diet interviewing, based on spouse interviews, diet diaries and 24-hour recall of diet in our Western New York Study; the interrelationships of herpes simplex virus 2, numbers of sex partners and other factors in cancer of the cervix in Los Angeles blacks and Chicanos; epidemiology of melanoma in 450 cases and 450 controls from RPMI. In addition, we wish to continue our ongoing data collection for the epidemiologic study of: cancer of the mouth, esophagus, stomach, larynx, colon, rectum, lung and bladder being carried out among all pathologically confirmed cases in Monroe, Niagara and Erie Counties and controls residing in the neighborhoods of cases; cancer of the testis and penis patients residing in New York State, as compared with controls residing in their neighborhoods; the interaction of oral contraceptives with other risk factors in the epidemiology of breast cancer; a prospective study of cancer among approximately 200,000 physicians and nurses in New York State, emphasizing diet. Throughout the period of study, we would carry on analyses of most of the above-named cancers for human genetics relationships.

Because many measures that can prevent or control cancer devolve from the epidemiology of those diseases and can involve changes in the human behavior, we are interested in the social and behavioral factors associated with cancer prevention and control. Thus, we wish to complete data collection in our study of the efficacy of breast self-examination (BSE) by comparing the proportion of breast cancer patients with advanced and early lesions who have practiced BSE. We also plan a study of lower-middle, upper-middle and rural residents of Erie County, building upon our earlier inquiry on blacks, to ascertain their knowledge of cancer.

BIBLIOGRAPHIC REFERENCES: Saxon Graham: Social Epidemiology and the Control of Cancer. Dominant Issues in Medical Sociology, Howard Schwartz and C.S. Kart, editors, 1978. Gregg Wilkinson, Edwin Mirand, Debra Walsh, John Wilson, Saxon Graham: Utilization of a Cancer Telephone Information Facility: A Comparison of Callers and Non-Caller Controls. The American Journal of Public Health 68:1211-1213 (1978).

152. STUDIES OF THERAPEUTIC END RESULTS AND PROGNOSTIC FACTORS

Myers, M. H., Stanek, E. J., Hankey, B. F., Prorok, P. C., Chen, J. S., Heise, H. W., Connelly, R. R., Baranovsky, A., Silverman, D. T., Devesa, S. S., Steinhorn, S. C., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Biometric Research & Analytic Studies Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

Ten-year follow-up results from the HIP study of screening for breast cancer have shown that the screened group experienced 1/3 less mortality from breast cancer than the control group. This reduction appeared to be concentrated in women over 50. The associations of cancer incidence with income and education were studied. Among whites, strong negative associations were observed for esophageal, stomach, lung and cervical cancer, with positive associations for colon, bladder and breast cancer. An analysis of TNCS and SEER data showed that for white males the incidence rate of mesothelioma has increased in recent years. The development of methodology for the evaluation of screening programs has demonstrated new age dependent characteristics of lead time and length bias. Appropriate variables to use in the analysis of randomized screening trials were defined. A study of suicides among cancer patients indicated that male patients were at twice their expected risk of suicide while females were not at excess risk. The relationship of the levels of selected urinary steroid metabolites to breast cancer recurrence subsequent to radical mastectomy was studied: relationships were observed only for postmenopausal patients.

BIBLIOGRAPHIC REFERENCES: Cutler, S.J., Myers, M.H., Steinhorn, S.C., and Flannery, J.T.: Gains in cancer treatment in the 1970's. Tufts Medical Alumni Bulletin, Tufts University School of Medicine, Medical Alumni Weekend and Reunion Days, Boston, Massachusetts, April 26-29, 1979. (In Press). Li, F.P., Myers, M.H., Heise, H.W. and Jaffee, N.: The course of 5-year survivors of childhood cancer. The J. Pediatr. 93: 185-187, 1978.

153. THE EFFECT OF HYSTERECTOMY ON MORTALITY FROM CANCER OF THE CERVIX

Miller, A. B., Lindsay, J., Wall, C., National Cancer Inst. of Canada, Epidemiology Unit, Dept. of Preventive Medicine & Biostatics, *c/o University of Toronto, Toronto, Ontario,* M5S 1A8, Canada

OBJECTIVE: To attempt to correct the effect of hysterectomy on mortality rates from cancer of the uterus for province by province data in Canada.

APPROACH: Previous work on mortality from cancer of the uterus (Int. J. of Cancer, 17, 602-672, 1976) did not include the effect of hysterectomy in the study population. Hysterectomies carried out for benign conditions would remove women from being at risk for cervical cancer and thus might explain the previously observed decline in mortality due to this disease. The current project will study this by repeating the analysis on national data in a province by province study.

On collaboration with Statistics Canada, data on the numbers of hysterectomies by one year age groups for women of ages 27-64, tabulated by province, will be used to estimate the number of women removed from being at risk. The available data will cover the period from 1969-1974. Thus, year by year the known population at risk in each age group can be adjusted to 'uteri at risk' instead of 'women at risk'. Using these corrected populations for the denominator, the mortality rates due to cervical cancer will be calculated on a province by province basis.

PROGRESS: The hospital morbidity data base of Statistics Canada is being used to produce initial tabulations of hysterectomies. Use of this data in the analysis of national cervical cancer data is expected to start in mid 1979.

154. EPIDEMIOLOGY OF CERVICAL DYSPLASIA

Morgan, R. W., Lickrish, G., University of Toronto, Dept. of Preventive Medicine & Biostatistics, *Medical Sciences Bldg., Toronto, Ontario,* M5S 1A8, Canada

OBJECTIVE: This project has two phases. Phase I encompasses the compilation and analysis of already existing data on approximately 1,800 patients seen at the Toronto General Hospital Dysplasia Clinic. This data will be used to generate hypotheses for Phase II, a case-control study designed to examine the relationship between cigarette smoking and dysplasia of the uterine cervix. Because of the recent evidence linking cigarette smoking and various types of cancer (including carcinoma of the uterine cervix) it is likely that exposure to cigarettes may also increase the risk of cervical dysplasia, a precursor to carcinoma of the uterine cervix.

APPROACH: Cases and controls will be drawn from three hospital clinics: the Dysplasia Clinic (cases), the Family Planning Clinic (controls), both from Toronto General Hospital, and the Dermatology Clinic (controls) from Women's College Hospital. Each case and control will be interviewed during regular clinic hours in the hospital. The questionnaire for the study will contain questions on demographic information (date of birth, education, income, race, marital status), a smoking history, age at first intercourse, number of sexual partners, and obstetrical and gynecological history, and questions on contraceptive practices.

155. STUDY OF RISK FACTORS IN CERVICAL CANCER

Galesanu, M. R., Carasevici, E., Inst. de Medicina si Farmacie, School of Medicine, Radiological Clinic, *Strada Universitatii 16, c/o Radiological Hospital, Iasi, Romania*

The purpose of the study is to establish possible correlations between the incidence of cervical cancer and some individual factors such as age at puberty, age at marriage, number of births and number of abortions. Such factors are found in rural areas where puberty and marriage occur at an early age, with numerous children. The studied population is taken from inpatients treated at the X-ray Clinic, Medical and Pharmaceutical Institute, Iasi, Romania. As about 400 new patients are admitted each year, we hope to study at least 2,000 cases within five years.

156. CARCINOMA IN SITU AND DYSPLASIA OF UTERINE CERVIX IN RELATION TO AGE, PARITY AND BEGINNING OF SEXUUAL RELATIONS

Masi, C. A., Ellena, A., Bertoli, R., Musacchio, R. M., Inst. Nacional Regional de Oncologia, Gynaecology Section, *Bv. Zavalla 3399, C.C. No. 366, 3000 Santa Fe, Argentina*

The aim is to determine the age at which carcinoma in situ and dysplasia occur for comparison with findings of authors elsewhere, using a sample group consisting of all 'healthy' patients seen at the Department of Gynecology. Data concerning the age at disease onset will be taken from the Registry. At the beginning of this study only age was considered; in the last months, parity and beginning of sexual relations have been added.

157. DYSPLASIA OF THE UTERINE CERVIX AND CANCER RISK

Oliveira, V. F., Sampaio Goes, J. E., Ferraz de Sampaio, L., Brazilian Research Inst., Dept. of Gynaecological Cancer Prevention, *Rua Florida 295 Vila Barcelona, Sao Caetano do Sul, Sao Paulo, Brazil*

The aim is to study cancer risk in patients with dysplasia of the uterine cervix using biopsy examination. Three hundred ninety-seven patients in whom colposcopy revealed atypical aspects - mosaic, punctation, leukoplasic or atypical vessels - were examined after three months, then every semester for two years, then yearly until completion of the research which covered the seven year period from 1972-1979. Of the 210 patients with slight dysplasia, 7 showed carcinoma in the subsequent examination (3.32%); of the 35 patients with moderate dysplasia and under 30 years of age, three presented carcinoma in the examinations that followed (8.57%); of the 84 patients with moderate dysplasia and over 30 years old, 13 presented carcinoma in the examination that followed (15.47%); of the 68 patients with acute dysplasia, 16 presented carcinoma in the examination that followed. Follow-up continues.

158. CANCER MORTALITY IN GUADALAJARA CITY

Garcia de Alba, J. E., Gonzales, M. R., Instituto Mexicano del Seguro Social, Depto. de Investigacion, *Belizario Dominguez Esquina, Apartado Postal 1-38-38, Guadalajara, Jalisco, Mexico*

This ongoing investigation of case characteristics is attempting to identify the host factors which might increase susceptibility to the cancers under study in Guadalajara, Jalisco. Guadalajara City contributes approximately 5 percent of the total cases of malignant neoplasms in the country, with an incidence rate of 45.12 per 100,000 inhabitants, as opposed to 36.0 per 100,000 inhabitants in the Mexican Republic. Cancer of the uterus and cervix accounts for 1/5 of malignant neoplasms in women and stomach cancer for 1/6 of the malignant neoplasms in men.

159. THE EFFECT OF CYNECOLOGICAL SCREENING PROGRAMS ON THE INCIDENCE OF CERVICAL NEOPLASIA

Lindberg, L. G., Ahlgren, M., Johnsson, J. E., University Hospital of Lund, Cytodiagnostic Laboratory, *E. Blocket, S22185 Lund, Sweden*

Cytological screening programs have a certain effect on the incidence figures of cervical neoplasia, both pre-invasive and invasive. However, a significant effect on mortality figures has been difficult to establish. Using a computerized program and the unique person identification number long accepted by everyone in Sweden, every single investigation and single individual can be easily followed. Preliminary figures indicate that a significant effect can be demonstrated much earlier than previously found among women actively taking part in a screening program.

160. COMPARATIVE EPIDEMIOLOGICAL STUDIES

Karacsony, I., Bartos, A., Onkologiai Gondozo Intezet, *Alkotmany u. 18, 8400 Ajka, Hungary*

International differences in cancer mortality in selected organs (lung, skin, stomach, breast, cervix uteri) are being studied with a view to developing causal hypotheses.

161. RISK OF CERVICAL CANCER AFTER A MASS SCREENING PROGRAM

Hakama, M. K., Pukkala, E., Tampere Yliopisto, Dept. of Public Health, *Vuolteenkatu 11, 33100 Tampere 10, Finland*

Mortality and incidence before and after a large-scale mass screening campaign are evaluated by specific risk indicators, and transition probabilities in the natural history of cervical cancer are estimated.

162. ANALYSIS OF CERVIX UTERI CANCER MORTALITY RATES IN CHILE

Dabancens, A., Pasternak, S., Universidad de Chile, Servicio de Citopatologia y Control de Cancer, *1058 Av. Bernardo O'Higgins, Santiago, Chile*

The study evaluates the National Cervix Uteri Cancer Control Programme. Standardized mortality rates for this cancer in different regions of the country are related to the percentage of women screened in these regions. A reduction of more than 70% in mortality rates, taking epidemiological factors into account, has been observed in the screened population. The rates per 100,000 for women over age 20 from 1970-1977 in two areas of Santiago show, for unscreened populations, expected rates of 27.90 and 24.54 and observed rates of 47.84 and 27.46, while in the screened populations expected rates are 17.40 and 19.43 and observed 4.64 and 5.71. The study continues.

163. ETIOLOGY OF CERVIX CANCER

Jain, S. P., Samuel, K. C., Singh, K. N., Jain, D. C., Pandey, U. C., J.K. Cancer Inst., Surgery, Chemotherapy, Pathology & Research Unit, *G.T. Rd., Kanpur 208002, Uttar Pradesh, India*

Cervix carcinoma has the highest incidence among malignant disease encountered at J.K. Cancer Institute, Kanpur. On an average 2,000 new patients are seen annually. More than 95% of the patients are of very low socioeconomic level. All have poor obstetrical histories, a large number of pregnancies and a serious offensive vaginal discharge for 20-30 years before the onset of cervix cancer. Data on socioeconomic status, number of pregnancies, vaginal discharge (including culture), cervical smear, colposcopy examination, etc. will be correlated statistically for both cervix cancer cases and women with vaginal discharge but no cancer. It is proposed to study about 200 cases per year. Emphasis will be on study of offensive discharge and its relationship to changes in the cervix.

164. STUDIES OF RADIATION-INDUCED CANCER

Land, C. E., Boice, J. D., Blot, W. J., Scotto, J., Stone, B. J., Beebe, G. W., Mason, T. J., Mendelsohn, L., Anderson, G. C., Kleinerman, R., Mundt, D. J., Greene, M. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Radiation Studies Section, *9000 Rockville Pike, Bethesda, Maryland, 20205*, United States of America

The objective of this project is to examine cancer incidence and mortality among populations exposed to ionizing and non-ionizing radiation, especially low-dose levels. As pressure mounted to identify the health effects of low-level radiation, a Radiation Studies Section was organized and large-scale studies of irradiated populations initiated. Groups studied include 80,000 Japanese A-bomb survivors, over 100,000 cervical cancer patients treated with radium implants, 20,000 former tuberculosis patients who received multiple chest fluoroscopies, 3,500 children exposed to head and neck irradiation, other patients exposed to diagnostic and therapeutic radiation, workers with histories of occupational exposures to radiation, and the populations of SEER reporting areas with different levels of solar UV radiation. In addition, project members have served on committees and task forces of DHEW, EPA, DOE, NIH, and NCI formulating government responses to current problems associated with health effects of ionizing radiation.

BIBLIOGRAPHIC REFERENCES: Boice, J.D., Jr., Land, C.E., Shore, R.E., Norman, J.E., and Tokunanga, M.: Risk of breast cancer following low-dose radiation exposure. Radiology 131: 589-597, 1979. Land, C.E. and Beebe, G.W.: Radiation-Induced Cancer in Atomic Bomb Survivors. In Margison, G.P., Ed.: Advances in Medical Oncology, Research and Education. Oxford, Pergamon Press, 1979, Vol. 1, Carcinogenesis, pp. 125-135.

B. EPIDEMIOLOGICAL STUDIES OF ENDOMETRIAL CANCER

165. UTERINE CANCER - COMPARATIVE STUDY OF URBAN AND RURAL WOMEN

Machado, J. C., Pinheiro, L. R., Tosello, J. R., Goes, J. C., Zyngier, S. B., Instituto Brasileira de Cont. Cancer, *Av. Alcantara Machado, Sao Paulo 2576, Sao Paulo, Brazil*

The Instituto Brasileiro de Controle do Cancer (IBCC) in collaboration with Fundacao Centro de Pesquisa de Oncologia (FCPO) undertakes a programme for uterine cancer detection and prevention in a large female population. Cytological tests are made on all women registered in the programme. Colposcopy and biopsy follow if dysplasia or carcinoma are detected on the first screening. Participants are interviewed and information on socioeconomic status, age, number of children, etc. is collected. The main objective is to make a comparative study of the prevalence of and conditions that contribute to uterine cancer in urban and rural women.

166. EPIDEMIOLOGY OF ANAPLASTIC ENDOMETRIAL CANCER

Kjellgren, O. R., Rydnert, J., Bjersing, L., Umea University, Dept. of Gynecological Oncology, *S90187 Umea, Sweden*

Following studies of corpus uteri cancer based on all patients in the northern part of Sweden (Acta Obstet. Gynecol. Suppl 65, 77-82, 1977) which defined risk factors such as age, body weight, menstrual and reproductive history, presence of fibroids, diabetes, hypertension, etc., anaplastic cancers occurring in the region are being compared with other corpus cancers to determine whether these characteristics are similar.

167. EPIDEMIOLOGICAL STUDY OF YOUNG PATIENTS WITH UTERINE CANCER

Masubuchi, K., Nemoto, H., Yamaguchi, S., Cancer Inst. Hospital, Dept. of Gynaecology, *1-37-1 Kamiikebukuro, Toshima-ku, Tokyo 170, Tokyo, Japan*

In recent years, there have been many reports on cervical cancer in young women. The objective is to study cervical carcinoma and corpus carcinoma in young patients epidemiologically. Among 6,336 cases of cervical carcinoma and 467 cases of corpus carcinoma treated in the Department of Gynaecology, the Cancer Inst. Hospital in Tokyo from 1949 to 1977, 873 patients with cervical carcinoma and 17 patients with corpus carcinoma were under 39 years of age and these are being analysed. Non-cancer patients operated on at the same time and of the same age are selected as a control group.

168. MORTALITY FROM UTERINE CANCER IN JAPAN

Nagai, M., Inst. of Public Health, Dept. of Public Health Statistics, *4-6-1, Shirokanedai, Minato-ku, Tokyo 108, Tokyo, Japan*

The mortality rate for uterine cancer in Japan has decreased over the last two decades. The 1977 rate is one-third that of 1955. Examination of the geographical distributions shows that the rate is higher in southwestern areas. Nationwide information regarding age at marriage and gestation, hygiene levels and socioeconomic status of population is being collected and correlated with death rates in an attempt to determine the reasons for the decrease and differences in geographical distribution.

169. CASE-CONTROL STUDY OF CARCINOMA OF ENDOMETRIUM

Shapiro, S., Boston University, School of Medicine, Dept. of Medicine, *80 E. Concord St., Boston, Massachusetts,* 02215, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

170. ANOVULATION AND EPIDEMIOLOGY OF HORMONE-RESPONSIVE TUMORS

Wallace, R. B., Sherman, B. M., Bean, J. A., Lifshitz, S., University of Iowa, School of Medicine, Dept. of Preventive Medicine & Environmental Health, *Jessup Hall, Iowa City, Iowa,* 52240, United States of America

This proposal is for continuation of our work investigating the etiology and pathogenesis of important hormonally responsive tumors using epidemiologic studies supported by relevant clinical endocrinologic investigations.

In years 07-09 of grant CA-15104, we propose to continue surveillance of a cohort of women who have prospectively recorded detailed menstrual cycle patterns and reproductive events for incident breast cancers. This is to determine if special antecedent patterns and events can be elucidated which are predictive of breast cancer and also yield clues to hormonal defects. In this cohort, we also plan to identify women who have undergone hysterectomy, obtain clinical and pathologic records, and correlate cycle patterns with benign uterine myomas.

We also propose a case-control study to further explore the etiology and pathogenesis of uterine myomas, an important cause of surgery and female morbidity in the U.S.A. Variables to be studied include menstrual and reproductive events implicated in breast, endometrial and cervical cancer, the use of medications including gonadal hormones and other drugs affecting prolactin secretion or the pituitary-ovarian axis, demographic and occupational features, and related systemic morbid events.

It is further proposed to explore our 'anovulatory hypothesis' among selected patients with myomatous disease in the case-control study. Differential levels of estrogen and progesterone receptors will be sought in tumor tissue and control myometrial tissue. Furthermore, to explore the possibility of luteal phase inadequacy among these patients, manifested by subnormal serum progesterone compared to estrogen levels, basal body temperatures and serum steroid hormone and gonadotropin levels will be checked through a menstrual cycle in a group of women with myomatous disease and an appropriate control group.

171. RELATION BETWEEN LONG-TERM DRUG USE AND UTERINE CANCER (HUMAN)

Jick, H., Boston University, School of Medicine, Dept. of Medicine, *80 E. Concord St., Boston, Massachusetts,* 02215, United States of America

This is part of a broader project. A summary of this subproject is not available.

C. EPIDEMIOLOGICAL STUDIES OF OVARIAN CANCER

172. MALIGNANT OVARIAN TUMORS IN BYELORUSSIA

Nikolaeva, D. V., Gomel Provincial Oncological Dispensary, Dept. of Radiological Gynaecology, *Sovietskaya 104, Gomel, Byelorussia, Union of Soviet Soc. Republics*

There has been no recent investigation into the incidence of ovarian cancer in Byelorussia. A geographical correlation study, which included data obtained from patients, has been carried out. Incidence was correlated with risk factors including chronic genital disease, surgery on pelvic organs after age 40, reproductive history and early menopause. There seemed to be differences in environmental risk factors among women over 40 in the northern compared to the southern part of the Republic. Analysis of the data continues, and it is proposed to set up a case-control study using two groups of over 1,000 age-matched controls from urban and rural populations.

173. EPIDEMIOLOGY OF OVARIAN CANCER

Smith, P. G., Beral, V. S., Imperial Cancer Research Fund, Cancer Epidemiology & Clinical Trials Unit, *9 Keble Rd., Oxford OX1 3QG, England, United Kingdom*

This is a case-control interview study with 200 cases and 400 matched controls (patients with other cancers and patients with non-malignant, non-gynecological conditions) to investigate risk factors for ovarian cancer with particular reference to reproductive factors (fertility and use of oral contraceptives).

174. TRENDS IN OVARIAN CANCER IN RELATION TO PATTERNS OF CHILDBEARING

Beral, V. S., Fraser, P. M., Chilvers, C. E., University of London, London School of Hygiene & Tropical Medicine, Dept. of Epidemiology & Med Statistics, *Keppel St., London WC1E 7HT, England, United Kingdom*

The present study is concerned with the analysis of routinely available mortality and morbidity data on ovarian cancer. The role of different patterns of childbearing on time and cohort trends, social class variation, and international variation in ovarian cancer is being investigated.

175. THE PATHOLOGY AND EPIDEMIOLOGY OF GERM CELL TUMORS

Marsden, H. B., Swindell, R., Birch, J. M., University Hospital of South Manchester, Dept. of Epidemiology & Social Research, *W. Didsbury, Manchester M20 8LR, England, United Kingdom*

This study was prompted by an increase in the incidence of these tumors, as assessed by the Manchester Children's Tumor Registry, which became significant in 1978. The pathology of all cases in this 25-year series, which include teratomas, yolk sac tumors and germinomas, has been reviewed to ensure diagnostic accuracy. The case-notes of each patient were carefully scrutinized for factors which may be of etiological importance and the mother's ante-natal records were also examined where these were available. These data are currently being analyzed. It is planned to extend this retrospective study to include cases in adults and a prospective case-control study of all cases aimed at the elucidation of etiological factors is also planned. Emphasis will be placed on determining the frequency of associated malformations and other tumors in the patients and their families and exposure to possible environmental carcinogens. Controls will be selected from the population and matched for age, sex and race.

176. THE INCIDENCE OF HISTOLOGIC TYPES OF MALIGNANT OVARIAN TUMORS IN NORWAY

Stalsberg, H., Blom, P., Bostad, L., Westgaard, G., Abeler, R. V., Segadal, E., Universitetet i Tromso, Inst. of Medical Biology, Morphology Unit, *P.O. Box 977, 9001 Tromso 2, Norway*

As part of an international comparative study sponsored by the UICC, the study will produce age-specific incidence rates for the various histologic types of malignant ovarian tumors in Norway. From listings provided by the Cancer Registry of Norway, histologic material from all cases of ovarian cancer diagnosed histologically in Norway during 1970-1972 has been collected. Each case will be classified independently by three pathologists according to the WHO Histological Typing of Ovarian Tumours. Analyses of intra- and inter-observer reproducibility will be included, as well as studies on type-specific prognosis.

177. CASE-CONTROL STUDY OF HIGH RISK FACTORS IN OVARIAN CARCINOMAS

Szamborski, J. J., Wacker Pujdac, B., Czerwinski, W., Gadomska, H., Akademia Medyczna w Warszawie, Inst. of Obstetrics & Gynaecology, Dept. of Pathomorphology, *Karowa 2, 00315 Warsaw, Poland*

The work published during the last years has shown some differences in prognosis and curability of ovarian carcinoma in relation to the histological type. The aim of this prospective study is to collect the clinical data concerning the biological status and previous gynecological history of patients with ovarian carcinoma and to explore the differences in these data between the patients with: serious carcinoma, mucinous carcinoma, endometrioid carcinoma and controls. Cancer-free patients attending the gynecological ward are used as controls. They are selected according to age to give a sample with approximately the same age structure as the ovarian carcinoma groups. The data is collected using a modified form of the ovarian tumour classification suggested by WHO. Subsequent analysis of possible risk factors will be undertaken.

178. OVARY NEOPLASMS

Boonyanit, S., Mahidol University, Siriraj Hospital & Medical School, Dept. of Obstetrics & Gynaecology, *2 Prannog Rd., Bangkok 7, Thailand*

Ovarian cancer has a relatively high frequency which is increasing rapidly. It ranks second in frequency among neoplasms of the female genital tract and as a cause of death among gynecological patients. An important problem is its asymptomatic course which entails a late diagnosis, high mortality rate, and inadequate results in therapy. The purpose of this study is to determine incidence, prevalence and mortality rates for ovarian neoplasms for the period 1970-1980. All new cases of ovarian cancer by year, period, district and age-group for the area of Bangkok and the provinces in the center of Thailand are included. The Thai people, the Chinese minority and other groups including Vietnamese, Cambodians, Moslems, and Indians will be studied. The influence of abortion, fertility, number of marriages, divorce rates, socioeconomic status and the effects of changes in the age distribution of the female population on the incidence rate in different districts, especially among people in industrial and agricultural areas and also among people from affluent residential districts, are being assessed. Occupation, heredity, drug intake, personal habits, culture, history of cancer among ancestors, and transsexual frequency are also studied.

179. STUDY OF OVARIAN CANCER IN GREATER WASHINGTON, D.C.

McGowan, L., George Washington University, School of Medicine & Health Sciences, Depts. of Obstetrics/Gynecology, *2121 Eye St. N.W., Washington, District of Columbia*, 20037, United States of America

Obtain the cooperation of staff at the designated hospitals in the Washington area. Identify all cases, aged 21-80, of ovarian cancer diagnosed between July 1, 1978, and June 30, 1981, in the designated hospitals. Select a number of controls approximately equal to the number of identified cases from each hospital of each race and age category. Contact the physician in charge of each case and each control to obtain his permission to approach the patient for an interview. Contact each patient whose physician has given permission to arrange an interview. Interview each respondent. Ask each respondent for release of specific medical information. Interview a sample of gynecologists and staff of fertility clinics. Validate a random sample of 20% of the interviews with patients. Record data from medical charts for cases and controls. Ask the pathologist for each case to allow one or more of the pathologic slides to be examined by the consulting pathologist for the study.

180. AN EPIDEMIOLOGIC STUDY OF CANCER OF THE OVARY

Hutchison, G. B., Scully, R. E., Cramer, D. W., Griffiths, C. T., Welch, W. R., Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

This epidemiologic study is designed to identify rsk factors for the several histologic types of ovarian cancer using case-control methodology. Exposures of specific interest are occupation, diet, medical and reproductive history, and drug use, particularly oral contraceptives and estrogens for menopause. Our goal is to identify risk factors that primarily may be modified to reduce disease ocurrence or that secondarily may be of clinical usefulness in defining the woman at risk for ovarian cancer, to achieve better control of the course of the disease.

181. EPIDEMIOLOGIC STUDY OF OVARIAN CANCER

Greenwald, P., Caputo, T., Richart, R., Nasca, P. C., Chorost, S., State Bureau of Cancer Control, Division of Epidemiology, *Empire State Plaza, Tower Bldg. Rm. 565, Albany, New York*, 12237, United States of America

Our general objective is to determine, by means of a concurrent case-control study, whether risks of developing various histologic types of ovarian cancer are influenced by: a) Prior reproductive experience of the patient, b) cancer among first degree female relatives, c) a combination of these factors. The hypothesis that low fertility or infertility contribute to risk will be refined and assessed. Also, we will have a systematically derived and validated statement of familial risk among first degree female relatives. Additional study variables will include prior hormonal therapy, pre-existing medical conditions and menstrual history.

In the proposed study, two population controls will be selected for each ovarian cancer patient interviewed. The controls will be matched by age and county of residence. Demographic and clinical data will be collected from hospital records of each ovarian cancer patient, and pathology slides reviewed. Various types of epidemiologic data will be collected through face-to-face interviews with each patient and control. Standardized follow-up procedures have been developed for verifying whether or not the relatives have ever been diagnosed as having or have died from a malignancy.

182. EPIDEMIOLOGY OF OVARIAN CARCINOMA

Mortimer, E. A., Heggie, A. D., Jones, P. K., Cramer, S. F., Case Western Reserve University, School of Medicine, Dept. of Community Health, *2109 Adelbert Rd., Cleveland, Ohio*, 44106, United States of America

The purposes of this study are to confirm and extend or refute certain previously obtained epidemiologic characteristics of ovarian carcinoma, and to see whether direct medical student involvement in epidemiologic research is feasible and productive. The epidemiologic characteristics of ovarian carcinoma to be studied include its higher rates in never-married women, women of low parity and women who have not used oral contraceptives. The study is intended to provide clues as to whether low parity is somehow conducive to, or non-protective for, ovarian carcinoma or whether some unknown ovarian defect predisposes both to sterility or low parity and ovarian cancer. In addition, the previously noted lower rates of a history of mumps, rubella and measles will be studied by serologic testing of patients with ovarian carcinoma and appropriate controls.

183. OVARIAN CARCINOMA IN ROCHESTER, MINNESOTA, 1935-1974

Annegers, J. F., Mayo Foundation, Dept. of Medical Statistics & Epidemiology, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

This is part of a broader project. A summary of this subproject is not available.

184. EPIDEMIOLOGICAL ASPECTS OF VULVAR CARCINOMA IN ISRAELI JEWISH PATIENTS

Menczer, J., Voliovitch, Y., Modan, B., Tel Aviv University, Sackler School of Medicine, Dept. of Obstetrics & Gynecology, *c/o Sheba Medical Center, Tel Hashomer, Israel*

While the low incidence of squamous carcinoma of the uterine cervix (SCC) in Jewish women is well known and other epidemiological aspects have been widely studied abroad as well as in Israel, no epidemiological studies of squamous carcinoma of the vulva (SCV) in Jewish women have so far been performed. The purpose of this investigation is to perform a population-based study of SCV in Israeli Jewish women in order to investigate whether epidemiological data with regard to age pattern, relative incidence and ethnic distribution follow data on squamous carcinoma of the uterine cervix in view of the multicentric origin concepts of malignancies of the lower genital tract.

D. EPIDEMIOLOGICAL STUDIES OF MULTIPLE GYNECOLOGICAL CANCERS

185. COMPARATIVE STUDY OF MORBIDITY AND RISK FACTORS OF FEMALE GENITAL CANCER IN THE GEORGIAN SSR, GERMAN DEMOCRATIC REPUBLIC AND POLAND

Charkviani, L., Lau, H. U., Gadomska, H., Gvamichava, D., Ministry of Health of the Georgian SSR, Dept. of Gynaecology, *Lake Lisi, Tbilisi 380077, Georgia, Union of Soviet Soc. Republics*

Comparative studies of morbidity rates for cancer of the main sites of the female genital tract will be carried out in the Georgian SSR, German Democratic Republic and Poland for the period of 1971-1980. Morbidity rates will be analyzed by age and histologial type. Analytical investigations will be carried out to identify risk factors. Each country will provide a certain number of questionnaires filled in for cases of gynecological cancer and for healthy controls. Comparative analysis of the morbidity rates and of the questionnaires from different countries will enable detection of risk factors.

186. CHORIONEPITHELIOMA AND GYNECOLOGICAL DRUGS

Yuasa, S., Sekine, S., Inst. of Public Health, Dept. of Epidemiology, *4-6-1, Shirokanedai, Minato-ku, Tokyo 108, Tokyo, Japan*

The number of deaths from chorionepithelioma in Japan from 1947 to 1976 was 6,432. Annual trends are being compared with those for live births, still-births (spontaneous and artificial), abortion, and production of vaginal contraceptive chemicals containing mercury, using data published officially by the Japanese government.

187. MALIGNANT NEOPLASMS OF FEMALE GENITAL ORGANS

Boonyanit, S., Vardthananusara, C., Mahidol University, Siriraj Hospital & Medical School, Dept. of Obstetrics & Gynaecology, *2 Prannog Rd., Bangkok 7, Thailand*

The study will describe trends in mortality from gynecological cancer in Thailand between 1970 and 1980, and incidence data collected by cancer registration since 1970. The data will permit study by area of residence, occupation, race, socioeconomic status, drugs used, customs, infections, and virus lesions in the genital tract. A retrospective case-control study of the role of estrogen therapy, particularly ethinyl estradiol, in the etiology of endometrial cancer is being undertaken on some 100-150 cases. Controls are non-cancer patients matched for age, parity, race and environment. Data on physical characteristics, obesity, diet, diabetes and other factors are obtained from cases and controls, using records of interviews and direct contact by home visits or correspondence.

188. RELATIONSHIP OF ABO BLOOD GROUPS TO CANCER IN BANGLADESH

Rahim, M. A., Miah, M. N., Sarma, S. K., Sirajoddowla, M., Khaleque, S. A., Kabir, A., Dacca Medical College Hospital, Dept. of Radiotherapy & Chemotherapy, *49 E. Azimpur Govt. Estate, Dacca 5, Bangladesh*

The study aims to examine the possible relationship of ABO blood groups to cancer of specific sites - stomach, salivary glands, breast cancer in both sexes, penis, cervix and bone. Normal healthy volunteers will act as controls.

189. PRE-MALIGNANT AND MALIGNANT GYNECOLOGICAL LESIONS IN PATIENTS TREATED BY IMMUNOSUPPRESSIVES

Baltzer, J., Eigler, J., Ludwig Maximilians University Munchen, Frauenklinik I, *Mainstrasse 11, 8000 Munich 2, Federal Republic of Germany*

Pre-malignant and malignant lesions are being sought in (1) patients with chronic renal insufficiency treated by dialysis without immnosuppressives; (2) patients on immunosuppressives following renal transplantation; (3) patients on immunosuppressives without renal insufficiency. Comparisons are made with gynecological out-patients.

190. CANCER IN THE IGBOS OF NIGERIA

Onuigbo, W. I., Medical Foundation, *8 Nsukka Ln., Uwani, P.M.B. 1098, Enugu, Nigeria*

This ongoing study of the relative frequency and the characteristics of cancer cases biopsied in different hospitals serving the Igbos of Nigeria and examined personally has resulted in the publication of data on tumors of the skin, eye, vulva, cervix, ovary, testis, alimentary tract, liver, oral cavity, lip and jaw. The most recent publications on tumors are: Schistosomiasis of ovarian thecoma (Med. J. Zambia, 12, 27-28, 1978) and adolescent breast masses in Nigerian Igbos (Amer. J. Surg., 137, 367-368, 1979). Work continues.

191. GYNECOLOGICAL NEOPLASMS IN IBADAN, NIGERIA

Junaid, T. A., Williams, A. O., University College Hospital, Dept. of Pathology, *Queen Elizabeth II Rd., Ibadan, Nigeria*

The study investigates the frequency, age distribution and clinicopathological correlations of histological types of tumors of the vulva, vagina, cervix, uterine body, ovaries and fallopian tubes in the cancer registry of the University College Hospital, Ibadan, Nigeria. All tumors will be subjected to histological review and reclassification. The tumors will be classified as suggested in the WHO monographs Nos. 10 and 13 on Histological Typing of Ovarian and Female Genital Tract Tumors.

192. CANCER EPIDEMIOLOGY IN TANZANIA, EAST AFRICA

Henschke, U., Luande, J., Muindi, J. N., Hiza, P. R., Phillip, J., Shaba, J., Mgaya, M., University of Dar es Salaam, Muhimbill Medical Centre, Dept. of Radiology & Radiotherapy, *P.O. Box 3592, Dar es Salaam, Tanzania*

Epidemiological studies, based on the national registry and on the registry of pathological specimens, including case studies of the most frequent cancers in Tanzania (cervix uteri, liver, skin in albinos, and stomach) are envisaged. Investigations of cancers which appear to be unusually frequent in relative terms (Burkitt's lymphoma, Kaposi's sarcoma, retinoblastoma) as well as of the cancers rare in East Africa, but frequent in Europe and North America (lung, colon, breast, pancreas, prostate) are contemplated.

E. GYNECOLOGICAL CANCER REGISTRIES

193. THE SWEDISH TWIN REGISTRY STUDIES

Friberg, L. T., Cederloef, R., Lundman, T., Floderus Myrhed, B., Karolinska Institutet, Dept. of Environmental Hygiene, *Solnavagen 1, S10401 Stockholm 60, Sweden*

In 1961 the Twin Registry covered about 10,000 same-sexed pairs born during the period 1886-1925. The registry was expanded in 1973 to include about 15,000 pairs born in 1926-1958. The aim of the Twin Registry is to study influences of the environment on morbidity and mortality, including cancer morbidity and mortality, based on periodical matching with the Swedish Cancer Registry. The latest updating was performed during 1979. The mortality data are evaluated through a continuous follow-up of mortality within the registries. The total twin program was reported in Acta Medica Scandinavia, Suppl. 612, 1977, in 'The Interactions of Smoking, Environment and Heredity and their Implications for Disease Etiology.' The latest report concerning cancer by Cederloef-Floderus, 'Cancer Mortality and Morbidity among 23,000 Unselected Twin Pairs'

(1979) dealt mainly with concordance rates for cancer of all sites and cervical cancers.

194. MULTIPLE PRIMARY MALIGNANT TUMOR SURVEY

Prior, M. P., Waterhouse, J. A., Saunders, V., Regional Cancer Registry, *c/o Queen Elizabeth Med. Ctr., Birmingham B15 2TH, England, United Kingdom*

An analysis of population-based data, collected at the Birmingham Regional Cancer Registry, is being carried out to determine whether there is any evidence of an increased risk of a second primary over that of a first, in terms of either site-specific associations or high-risk groups. The results may help to define aetiological factors in tumour development and to identify individuals 'at risk' who will benefit from increased surveillance. The method of analysis is similar to previous surveys in that an index site is selected, and observed numbers of second primary tumours are compared with expected numbers computed from incidence rates for the regional population. Special consideration has been given to fundamental methodology related to coincidental diagnoses and to the sequence of tumours. The emphasis has been, therefore, on 'site-pair' analysis, that is on investigating each sequence for a pair of sites, in contrast to the conventional approach which considers one index site in relation to all second primary sites. A major survey of bilateral breast cancer over a period of nearly 30 years has been undertaken and the interrelationships between breast and female reproductive sites have been investigated. Current work includes analyses for lung in association with male reproductive sites, and also with bladder. Future projects will include the addition of large bowel tumours to the spectrum of paired analyses.

195. GYNECOLOGICAL TUMOR REGISTRY

Daw, E. G., North Manchester General Hospital, Dept. of Obstetrics & Gynaecology, *Crumpsall, Manchester M8, England, United Kingdom*

All gynecological tumors seen in the northern district of Manchester are registered using a standard registration form. The data collected are subjected to systematic review. A prospective review of chemotherapy regimes used for carcinoma of the ovary is being undertaken, as well as a retrospective review of carcinoma of the cervix and corpus uteri.

196. GYNECOLOGICAL CYTOLOGY REGISTRY, NOVA SCOTIA

Bisson, G., Robinson, S. C., Fraser, R. C., Victoria General Hospital, *5788 University Ave., Halifax, Nova Scotia*, B3H 2Y9, Canada

A computerized gynecological cytology registry has been designed for the Province of Nova Scotia. The objectives of the registry are as follows: (1) To provide complete and accurate information regarding the numbers and location of women being screened and the number of Papanicolaou smears being examined annually throughout the Province of Nova Scotia; (2) to provide information for use in the establishment of a province-wide quality control program in the area of gynecological cytology; (3) to provide a comprehensive province-wide system of follow-up of cases who have abnormal cytology; (4) to provide epidemiological data related to malignant and pre-malignant disease of the uterus in the Province of Nova Scotia. Data are being collected from all laboratories providing a gynecological cytology service in the Province of Nova Scotia using standardized diagnostic terminology and a standardized requisition report form. The design of the computer program will provide annual and semi-annual reports relating to the numbers of women being screened in the province by age and county distribution. Information regarding abnormal smears and subsequent colposcopy and biopsy findings are also incorporated in the routine computer printout. Since Nova Scotia has a relatively small and stable population of approximately 300,000 women at risk of developing cervical neoplasia, it is hoped that the program will provide useful information in relation to the distribution and epidemiology of this disease in this population.

197. GYNECOLOGICAL CYTOLOGY REGISTRY, NOVA SCOTIA

Anderson, G., Robinson, S. C., Fraser, R. C., Victoria General Hospital, *5788 University Ave., Halifax, Nova Scotia*, B3H 2Y9, Canada

A computerized gynecological cytology registry has been designed for the Province of Nova Scotia. The objectives of the registry are as follows: (1) To provide complete and accurate information regarding the numbers and location of women being screened and the number of Papanicolaou smears being examined annually throughout the Province of Nova Scotia; (2) to provide information for use in the establishment of a province-wide quality control program in the area of gynecological follow-up of cases who have abnormal cytology; (4) to provide epidemiological data related to malignant and pre-malignant disease of the uterus in the Province of Nova Scotia. Data are being collected from all laboratories providing a gynecological cytology service in the Province of Nova Scotia using standardized diagnostic terminology and a standardized requisition report form. The design of the computer program will provide annual and semi-annual reports relating to the numbers of women being screened in the province by age and county distribution. Information regarding abnormal smears and subsequent colposcopy and biopsy findings are also incorporated in the routine computer printout. Since Nova Scotia has a relatively small and stable population of approximately 300,000 women at-risk of developing cervical neoplasia, it is hoped that the program will provide useful information in relation to the distribution and epidemiology of this disease in this population.

198. VIENNESE GYNECOLOGICAL TUMOR REGISTRY

Breitenecker, G., Seidl, A., Universitat Wien, Medizinischen Fakultat, *Spitalgasse 23, 1010 Vienna, Austria*

In Austria, gynecological tumors are the cause of 20% of all deaths of females from cancer. At present some one million vaginal smears are examined in Austria annually. However, the number of women screened is not known as there is no registration of individuals and no record is kept of frequency of repeated examinations. Only inaccurate figures are available on the prevalence and incidence rates of gynecological cancers and, although mortality statistics provide the most reliable existing data, these cannot be used for epidemiological investigations as the localization of uterine cancer is not reported in nearly two-thirds of cases, so that the annual death rate for women with cervical cancer versus endometrial cancer is not clear. The aim is to organize a gynecological tumor registry in the Viennese area, which could eventually form part of a state-wide cancer registry. In addition to improving mortality and morbidity data and determining incidence and prevalence rates and effectiveness of treatment, there will be patient-based registration of cytological reports to determine prevalence and incidence rates of pre and early stages of cervical cancer and to evaluate screening programs. Cooperation with federal and community institutions, the Austrian League Against Cancer and gynecological and pathological institutes and practitioners will be extended.

199. INTERNATIONAL COOPERATIVE PROGRAM FOR COMPARATIVE STUDIES IN NEIGHBORING REGIONS OF AUSTRIA, CZECHOSLOVAKIA, HUNGARY, YUGOSLAVIA

Wrba, H., Karrer, K., Friedl, H., Plesko, I., Peter, Z., Eckhardt, S., Kocsis, S., Tichy Racs, M., Ravnihar, B., Pompe Kirn, V., Universitat Wien, Inst. Fuer Krebsforschung, *Borschkegasse 8A, A1090 Vienna, Austria*

A cooperative program has existed since 1972 between Hungary and Austria in cancer epidemiology. For Austria, the Burgenland Region on the Hungarian border is of particular interest, as previous epidemiological studies have shown that stomach cancer mortality is strikingly higher there than in the remainder of Austria. Further, the neighboring regions of Hungary and Austria are particularly suitable for comparative epidemiological studies, as the ethnic origin of the population of these regions is very similar. (The county of Burgenland belonged to Hungary until 1921.)

Morbidity data for the following sites were examined from 1969 onwards - stomach, colon, rectum, lung, female breast, cervix and corpus uteri. It is intended to analyze the data and to extend the study to a larger geographical area. Since February 1976 the Cancer Registry of Slovenia, Yugoslavia has collaborated in this project and provides the pertinent data for the Pomurje district which borders both Austria and Hungary. Finally, the region of Bratislava, Czechoslovakia joined the study in 1978, also with morbidity data from 1969 onwards.

200. EPIDEMIOLOGY OF GYNECOLOGICAL CANCER OF THE SAARLAND

Sachs, H., Grelich, F., Universitaets Frauenklinik, *D6650 Homburg, Saarlands, Federal Republic of Germany*

Time trends in gynecological cancer are being evaluated using the data of the Saarland Cancer Registry.

201. FREQUENCY OF SELECTED CANCERS

Isarangkul Na Ayuthya, W., Bhamarapravati, N., Mahidol University, School of Medicine, Dept. of Pathology, *Bangkok*, 7, Thailand

A computerized tumor data base has been implemented to permit instant retrieval of selected diagnoses. At present all the tumor data from 1974 to 1978 have been processed. A project has been designed to study relative frequencies and age distributions of primary cancers of all sites from 1974 to 1978, with an emphasis on female genital tract cancers. Computer programs have been prepared to facilitate automatic tabulation of the frequencies of specific types of cancers as well as the overall frequency of all cancers of a particular site. Age distribution will also be obtained automatically.

202. INFORMATION SYSTEM FOR RETRIEVAL OF GYNECOLOGIC MALIGNANCY

Buchler, D. A., University of Wisconsin, Madison Campus, Center for the Health Sciences, *500 Lincoln Dr., Madison, Wisconsin*, 53706, United States of America

This is part of a broader project. A summary of this subproject is not available.

203. EARLY DETECTION OF BREAST AND CERVIX CANCER

Teixeira Fernandes, R., Hospital de Aeronautica de Campo Grande-MS, Servicio de Tocoginecologia, *Av. Duque de Caxias 2905, Est. Mato Grosso do Sul, Campo Grande DEP 79100, Brazil*

OBJECTIVE: To teach basic health education concerning breast self-examination and yearly or biannual preventive examinations (including clinical breast exam, cervical cytology, colposcopy and gynecological exam) to patients determined to be at high risk of developing breast or cervix cancer. This constitutes a continuing program of prevention and early detection of cancer.

APPROACH: Patients are registered and undergo an oral orientation on the topic. They receive written instructions regarding hygenic care and prevention of precursory lesions, etc.

Clinical breast exam and gynecological examinations are performed, including cytology and colposcopy. Breast biopsy and/or cervical biopsy are performed when needed and therapeutic measures are instituted in cases of precursory lesions such as cervical dysplasia, benign mammary lesions including breast adenosclerosis. Patients are coded into high-risk groups for breast and cervix cancer.

204. PROFESSIONAL EDUCATION IN CYTOLOGY RELATED TO CANCER

Blair, O., St. Louis University, School of Medicine, *1402 S. Grand Blvd., St. Louis, Missouri*, 63104, United States of America

OBJECTIVE: Provide for a three-year agreement to develop and conduct an educational training program to advance the use and value of cytology in bladder, lung, colorectal, and cervical cancer. The Contractor is required to develop and conduct this training program, and to participate in the Steering Committee Meetings, provide semi-annual written reports of progress and problems, provide written preliminary final report to be submitted for review by the Project Officer, and submit revised final report based on Project Officer's review of preliminary report.

205. PROFESSIONAL EDUCATION IN CYTOLOGY

Barker, E. A., University of Washington, School of Medicine, Dept. of Pathology, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

OBJECTIVE: Provide a three-year agreement to develop and conduct an educational training program to advance the use and value of cytology in bladder, lung, colorectal, and cervical cancer. The Contractor is required to develop and conduct this training program; in addition, to participate in the Steering Committee Meetings, provide semi-annual written reports of progress and problems, provide written preliminary final report to be submitted for review by the Project Officer, and submit revised final report based on Project Officer's review of preliminary report.

III. STUDIES OF TROPHOBLASTIC NEOPLASMS

206. PROSPECTIVE STUDY OF GESTATIONAL TROPHOBLASTIC DISEASE IN THE NETHERLANDS

Stolk, J. G., Kenemans, P., Vooijs, P. G., Houx, H., Franke, H. R., Vrije Universiteit te Amsterdam, Dept. of Obstetrics & Gynecology, *Amsterdam, Netherlands*

The main objective is to study the incidence of gestational trophoblastic neoplasms in the Netherlands, and to improve the prognosis of choriocarcinoma by early therapy. Cases of molar pregnancy will be registered and beta-subunit human chorionic gonadotropin determinations in all cases will be carried out in one laboratory (Dr. Houx).

207. DIAGNOSIS AND CONTROL OF PATIENTS WITH TROPHOBLASTIC DISEASE BY THE QUANTIFICATION OF HUMAN CHORIONIC GONADOTROPIN (ABBREV)

Masi, C. A., Ellena, A. N., Musacchio, R. M., Inst. Nacional Regional de Oncologia, Dept. de Ginecologia, *Bv. Zavalla 3399, C.C. No. 366, 3000 Santa Fe, Argentina*

OBJECTIVE: To utilize serial immunological and biological determinations of HCG in patients with trophoblastomas as an auxiliary element in diagnosis and a criterion of cure.

METHODS: The serial quantification by immunobiologic methods is used as an auxiliary reference in the diagnosis of patients who might have trophoblastic disease. In those already treated for the above-mentioned pathology, HCG is titrated (with hypophyseal block) using biological methods (modified Albert).

208. EPIDEMIOLOGY OF GESTATIONAL TROPHOBLASTIC DISEASES IN IBADAN, NIGERIA

Junaid, T. A., Aimakhu, V. E., Adeleye, J. A., University College Hospital, Dept. of Pathology, *Queen Elizabeth II Rd., Ibadan, Nigeria*

Previous studies have confirmed the relatively high frequency of hydatidiform mole and choriocarcinoma in Ibadan, Nigeria and have contributed to their diagnosis and clinical management. The aim of the present study is to collate epidemiological data including correlation of incidence with climatic conditions, time of year, blood group, ethnic groups, use of oral contraceptive and others that may be of aetiologic significance.

209. OCCURRENCE AND FOLLOW-UP OF TROPHOBLASTIC NEOPLASIA IN CHIBA PREFECTURE

Takamizawa, H., Kudo, J., Sekiya, S., Kato, T., Endo, N., Chiba University, School of Medicine, Dept. of Obstetrics & Gynecology, *313 Inohanacho, Chiba, Chiba, Japan*

Since 1973, more than 1,000 patients with hydatidiform mole have been registered at the Trophoblastic Neoplasia Registry of our Department. Of these, about 10% had trophoblastic neoplasia. A total of 112 patients (27 with choriocarcinoma, 27 with invasive mole, and 58 histologically unclassified) were treated in our Chiba University Hospital. At present, the remission rate of low-risk patients is 100%, whereas that of high-risk patients diagnosed according to the criteria of Hammond et al. (Am. J. Obstet. Gynecol., 115: 451, 1973) is only about 60%. High-risk patients were treated with combination chemotherapy consisting of methotrexate 15 mg/day, actinomycin D O.35 mg/day, and cyclophosphamide 100 mg/day. All three drugs were administered daily for 5 days per course with an interval between courses of 10 to 14 days.

We are now studying the establishment of more effective combination chemotherapy for 'poor-prognosis' high-risk patients.

210. TROPHOBLASTIC DISEASE - CLINICAL AND IMMUNOLOGICAL

Brewer, J. I., Northwestern University, Chicago Campus, School of Medicine, Dept. of Obstetrics & Gynecology, *303 E. Chicago Ave., Chicago, Illinois,* 60611, United States of America

The proposed project is a multidisciplinary study of trophoblastic disease. Chemotherapy trials in high risk and in metastatic choriocarcinoma using untried agents and adjuvant radiation therapy will be conducted. In low risk patients, alternating methotrexate and actinomycin D will be employed. HLA-A,B,C,D and B cell (Ia) typing will done. A study will be made of our observation that patients' sera enhances rather than inhibits in mixed lymphocyte culture response and to study factors relating to this stimulating ability. The effect of peripheral blood lymphocytes and their products on excretion of hCG by tissue culture cell lines will be investigated. The carboxyl terminal hCB B tryptic peptide method will be used to measure hCG-like substances in the sera and urine of patients with trophoblastic disease and to compare these with levels measured by hCG/LH and specific hCG methods.

211. CHORIOCARCINOMA CHEMOTHERAPY (HUMAN)

Brewer, J. I., Northwestern University, Chicago Campus, School of Medicine, Dept. of Medicine, *303 E. Chicago Ave., Chicago, Illinois,* 60611, United States of America

This is part of a broader project. A summary of this subproject is not available.

212. HL-A ANTIGENS IN WOMEN WITH TROPHOBLASTIC NEOPLASMS

Lewis, J. L., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

213. MODEL REGIONAL TROPHOBLASTIC DISEASE PROGRAM

Morrow, C. P., Schlaerth, J. B., Nalick, R. H., Yordan, E. L., Wallace, D. L., O'Brien, T. J., d'Ablaing, G., Gaddis, O., Shen, J., Townsend, D. E., University of Southern California, School of Medicine, Dept. of Obstetrics & Gynecology, *2025 Zonal Ave., Los Angeles, California,* 90033, United States of America

The Gynecologic Oncology Program encompasses all of the professional, educational, and research activities of the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Southern California/Los Angeles County Medical Center. This division has distinguished itself in each of these areas of gynecologic oncology despite its setting within a county facility with very limited funds and a large patient service responsibility. The division's many achievements can be attributed to several factors, the most important of which are a talented, dedicated staff and funding from outside the county government and University, the majority of which has been derived from NIH sources.

The primary objectives of our oncology program are: (1) To continue the outreach programs: a) Pap screening of high risk, indigent women in the Los Angeles area (Porta Pap Project), b) hCG and consultative service for trophoblastic disease in the western states (Trophoblastic Disease Program), and c) the registration, examination and follow-up of women exposed to stilbestrol in utero (DESAD project). (2) To provide optimal diagnostic and therapeutic care for our patients with pre-invasive and invasive gynecologic cancers at this medical center. (3) To continue to improve cancer education for our patients, medical students, interns, residents, and community physicians through lectures, publications, postgraduate programs, seminars, and bedside teaching. (4) To educate physicians who will become cancer educators in academic and community environments. (5) To provide expert consultative services to the community physicians. (6) To work toward better cancer diagnosis and management by continuing to improve our clinical and applied laboratory research in gynecologic oncology in this university setting with its large patient population.

214. REGIONAL TROPHOBLASTIC DISEASE CENTER

Hammond, C. B., Tyrey, L., Duke University, School of Medicine, Dept. of Obstetrics & Gynecology, *Box 3711, Durham, North Carolina,* 27710, United States of America

The overall objective of this project is to enhance available care for patients with malignant trophoblastic disease. This is to be accomplished by expansion of a regional center, serving the southeastern United States, which provides clinical and laboratory expertise to aid community physicians caring for patients suspected or known to have gestational trophoblastic disease. The primary goal of this project is expansion of quality care available to all patients carried out through educational efforts directed towards community physicians, by the prompt availability of consultative support, by accurate and available sensitive hCG assays, and by provision of an inpatient treatment center for physicians who would like to utilize these services for patients with these diseases.

BIBLIOGRAPHIC REFERENCES: Cerebral Metastatic Choriocarcinoma - Intensive Therapy and Prognosis, John C. Weed, Jr. and Charles B. Hammond, Obstetrics and Gynecology, 55:89-94, 1980. Alpha Subunit of HCG in Sera of Choriocarcinoma Patients in Remission Martin M. Quigley, Lee Tyrey, and Charles B. Hammond, JCEM, 50:98, 1980.

215. GROWTH OF HUMAN TROPHOBLASTIC CELLS IN CULTURE

Haughom, J. R., Flow Lab. Inc., *1710 Chapman Ave., Rockville, Maryland,* 20852, United States of America

The contractor shall prepare, maintain, and store at low temperature human trophoblastic cells. Specifically, he shall grow in enriched media clonal lines of trophoblasts derived from choriocarcinoma, normal placenta, or virally (SV-40) transformed placental cells.

216. THE DEVELOPMENT AND PATHOLOGY OF HUMAN CHORIOCARCINOMA

Friedman, S. J., Skehan, P. J., Vatter, A. E., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Pharmacology, *4200 E. 9th Ave., Denver, Colorado,* 80262, United States of America

The objectives of the proposed research are: 1. to understand the molecular mechanisms of malignant trophoblast differentiation; and 2. to elucidate the role of giant multinucleated syncytiotrophoblast-like cells in the physiopathology of choriocarcinoma. The proposed studies include: 1. mechanisms of multinucleation; 2. cytodifferentiative changes in membrane and cell surface properties; 3. role of adhesion in cytodifferentiation.

217. A MODEL FOR INDUCTION OF CHORIOCARCINOMA IN THE RAT

McCormack, S. A., Baylor College of Medicine, School of Medicine, Dept. of Cell Biology, *1200 Moursund Ave., Houston, Texas,* 77025, United States of America

The purpose of this research is to develop a model for the induction of choriocarcinoma from normal rat trophectoderm. The inductive procedure consists of fetectomy, prolongation of the luteal phase, and administration of a carcinogenic drug. Fetectomy arrests the normal differentiation of the placenta. If fetectomy is carried out before gestation day 12, the placenta persists composed almost entirely of basal zone trophectoderm in which the percentage of trophoblast giant cells is also increased. Choriocarcinoma can be induced on this substratum by carcinogenic drugs. The time necessary for induction is gained by prolongation of the luteal phase with administered progesterone. Progression of normal to malignant cells will be monitored by studies of the endocrine function of the persisting trophectoderm, the ontogeny of hormone receptors, and aberrations in the interactions of the trophectoderm with uterine cells in vivo and as monolayers in vitro. Any tumors developed will be used in an attempt to culture a cell line from rat choriocarcinoma which can be characterized and used for in vitro studies. The correlation of these data will provide facts which may help explain the control of the trophectoderm through the essential but potentially destructive invasive processes of normal implantation and the mechanisms which have failed when choriocarcinoma develops.

218. MODEL FOR THE STUDY OF TROPHOBLASTIC NEOPLASIA

Boots, L. R., University of Alabama in Birmingham, School of Medicine, Dept. of Obstetrics & Gynecology, *1919 7th Ave. S., Birmingham, Alabama,* 35233, United States of America

The purpose of this project is first, to develop an animal model (rat) in which trophoblastic neoplasia can be studied and second, to study biochemial changes in the trophoblast and adjacent uterine tissue during induction and growth of the tumor. Trophoblastic neoplasia is induced with DMBA in fetectomized 12-day-pregnant rats. The presence of the tumors will be detected by assaying blood levels of rat chorionic mammotropin (RCM). Subsequently, growth characteristics will be related quantitatively to levels of RCM and key glycolytic, tricarboxylic acid cycle and pentose phosphate enzyme activities will be determined. The effects of varying levels and ratios of sex steroids, synthetic sex steroids and chemotherapeutic agents on RCM levels and biochemical parameters will also be determined. The major thrust of this project is to study these parameters in vivo, in relation to the animal model and subsequently, to utilize cell culture and other in vitro techniques as they may apply.

IV. TERATOCARCINOMAS

A. BIOCHEMICAL CHARACTERISTICS OF TERATOCARCINOMAS

219. CHARACTERIZATION OF MALIGNANT CELLS IN VITRO

Tveit, K. M., Fodstad, O., Olsnes, S., Norsk Hydros Inst. for Cancer Research, Dept. of Biochemistry, *Montebello, Oslo 3, Norway*

OBJECTIVE: To characterize and study the growth properties of a human teratocarcinoma and a human melanoma cell line.

APPROACH: The tumors are grown in nude mice and then transferred to cell culture.

PROGRESS: Some data indicate that the human teratocarcinoma may have hybridized in vivo with mouse cells. Isoenzyme studies, chromosome analyses and biochemical studies of the tumors are used in attempts to establish whether this is indeed the case.

A human malignant melanoma shows abnormal growth properties in vitro. It is rapidly dividing and grows in shaker suspension cultures as well as in monolayers. The cells are aneuploid, the chromosomes are clearly human and the isoenzyme patterns are entirely of the human type.

220. HIGH MOLECULAR WEIGHT, EXTRACELLULAR MATRIX GLYCOPROTEINS SYNTHESIZED BY ENDODERM CELLS

Hogan, B., Imperial Cancer Research Fund, Cell Biology Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Work has continued on the characterization of the two extracellular matrix glycoproteins synthesized in large amounts by the teratocarcinoma-derived parietal endoderm cell line PYS-1. The proteins, called PYS A and B, have molecular weights of 350K and 220K daltons, respectively, on SDS gels under reducing conditions. They are resistant to collagenase and are immunoprecipitable by rabbit antiserum raised against teratocarcinoma embryoid bodies but not by antifibronectin antibodies. The possibility is being tested that A and B are the same as the recently described basement membrane glycoprotein, laminin, which is synthesized as a 400K dalton precursor and cleaved to two 200K components (Timpl et al., Journal of Biological Chemistry, in press). Normal parietal endoderm cells isolated from 10 1/2-day mouse embryos synthesize large amounts of A and B and incorporate them into the underlying basement membrane (Reicherts' membrane). Isolated visceral endoderm and mesoderm cells produce very little A and B and no synthesis can be detected in undifferentiated embryonal carcinoma stem cells. A and B are being used as biochemical markers with which to follow in vitro the differentiation of teratocarcinoma stem cells into parietal endoderm.

221. TERATOCARCINOMA METASTASIS AND EMBRYOLOGICAL CORRELATIONS

Kahan, B. W., University of Wisconsin, Madison Campus, School of Letters & Science, Dept. of Zoology, *500 Lincoln Dr., Madison, Wisconsin*, 53706, United States of America

Embryonic development involves complex cellular interactions which are probably mediated in part by changing cell surface molecules. Seriological reagents detecting antigenic differences between cells are highly sensitive probes for the indentification and analysis of these surface molecules. Hybridoma cells producing monoclonal antibodies directed against embryonic determinants will be produced, using as immunogens teratocarcinoma cells having defined preferential differences in the in vitro cell adhesion and in vivo metastatic patterns.

Antigenic determinants characteristic of these different types of teratocarcinoma cells will be determined, and their role in the different functions of these cells examined. The presence of these determinants and their significance in early embryogenesis will be studied, by techniques including immunofluorescence and analysis of antibody Fab fragments on developing embryos.

Analysis of the importance of these determinants will also include the derivation of mutant teratocarcinoma cells lacking these antigens, and the functional comparison of antigen-positive and antigen-deficient teratocarcinoma cells in in vitro and in vivo cell association patterns.

222. THE ROLE OF THE EXTRACELLULAR MATRIX IN TERATOGENESIS AND EMBYROGENESIS

Linsenmayer, T., Little, C. D., Massachusetts General Hospital, Developmental Biology Lab, *32 Fruit St., Boston, Massachusetts*, 02114, United States of America

Recent work described a procollagen produced by both a teratocarcinoma (TSD4) and a mouse blastocyst (MB4) derived cell line. One objective of this proposal will be to determine the time and place of biosynthesis of TSD4/MB4 procollagen in both teratocarcinomas and normal mouse embryos. The second objective will be to test the possibility that certain embryonic inducing tissues will influence the determination of the pluripotent stem cells of teratocarcinomas (embryonal carcinoma).

Regarding the first objective, the specific aims will be: 1. To use purified TSD4/MB4 procollagen as an antigen to obtain an antisera. 2. To affinity purify the antisera and demonstrate monospecificity. 3. To examine by indirect immunofluorescent staining, histological sections of representative stages of both mouse embryos and teratocarcinomas.

Regarding the second objective the specific aims will be: 1. To culture embryonal carcinoma cells and embryoid bodies in the presence of chick and mouse notochord, neural retina and limb bud mesenchyme. 2. To graft composits of embryonal carcinoma cells and embyroid bodies and the above inducing tissue on the chorioallantoic membrane (CAM) of chick. 3. To examine the CAM grafts by indirect immunofluorescence staining with antisera to various extracellular matrix proteins as a means of measuring the influence of the inducing tissues.

223. SURFACE CHEMISTRY OF TERATOCARCINOMA AND EMBRYOS

MayliePfenninger, M. F., Bennett, D., Columbia University, College of Physicians & Surgeons, Dept. of Anatomy, *630 W. 168th St., New York, New York*, 10032, United States of America

Our recent serological work on embryonal carcinoma cells and embryos carrying mutant genes at the T/t locus has provided evidence that changes in cell surface antigens occur as development proceeds, and that abnormal surface components can be responsible for abnormal forms of embryonic differentiation that may result in malignancy. In this project we intend to begin to examine the molecular nature of cell membrane-associated molecules that may play a role in mediating morphogenetic events. Carbohydrate-containing components and glycosyltransferases at the cell surface have both been theoretically implicated in cell recognition and cell interactions. We plan therefore to compare cells of three types, namely normal embryonic cells, teratocarcinoma cells, and mutant embryonic cells whose differentiation is blocked, with respect to cell surface representation of these components. These three cell types will be compared with respect to: (1) their binding capacity for a battery of specific lectins; (2) the topology of lectin binding; (3) their representation of membrane-bound glycosyltransferase, and (4) their plasmalemmal content of glycoproteins. This should enable us to define differences between normal embryonic cells and embryonic cells that are abnormal either because of malignancy or mutational effects that interfere with differentiation. This is a first step toward identifying molecules at the cell surface that are crucial for cell interactions.

224. TERATOCARCINOMA AND EMBRYONAL TUMORS - SURFACE ANTIGENS

Artzt, K., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This application proposes to follow serologically embryonic surface antigens in the mouse that are characteristic of specific early stages of cell differentiation both in the embryo and on embryonal tumor cells, specifically teratocarcinoma and a genetically caused medulloblastoma-neuroblastoma. The project will make use of a series of mutant genes at the T-locus which are known to: 1) Interfere with differentiation at specific times in development, 2) specify cell surface antigens on sperm and in the embryo, and 3) in the one case studied, cause an embryonal tumor. We would like to know the time course of the expression of these antigens, if they are functional, and what role the mutant form of the antigen plays in malignant differentiation. These objectives involve transplantation of mutant embryos, obtaining transplantable tumors from t-mutant cells, and serological definition of embryonic surface antigens by means of cytotoxicity tests and absorption studies.

225. IMMUNOLOGIC INVESTIGATION OF HUMAN BLADDER AND KIDNEY CANCER

Hakala, T. R., Ballou, B. T., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *University Dr. C, Pittsburgh, Pennsylvania*, 15240, United States of America

The investigation of hybridoma anti-tumor antibodies as reagents for cytotoxicity and tumor localization now confirms that the anti-teratoma hybridoma antibody is capable of localizing teratocarcinoma in the murine host. Enzymatic modification of the antibody decreases the non-specific uptake by non-tumor organs and increases the excretion of tumor unbound antibodies. These developments indicate that the application for detection of tumors in humans may be warranted since the enzyme modified antibody would reduce irradiation to the host and the studies in vitro indicate that the murine anti-tumor antibody reacts against human teratocarcinoma.

Studies designed to estimate the risks to human tumor patients by use of these radio-labeled anti-tumor antibodies are under way in preparation for requesting permission for trials in patients with teratocarcinoma.

B. DIFFERENTIATION OF TERATOCARCINOMAS

226. DIFFERENTIATION OF MURINE TERATOCARCINOMA CELLS IN CULTURE

McBurney, M. W., University of Ottawa, Dept. of Biology, *30 Somerset St. E., Ottawa, Ontario*, K1N 6N5, Canada

OBJECTIVE: The object of this research program is to investigate some of the cellular and molecular events which occur during the differentiation of murine teratocarcinoma cells in culture. Particular attention is to be paid to the differentiation of the X chromosome in female teratocarcinoma cells.

APPROACH: Two teratocarcinoma cell lines which contain two X chromosomes have already been investigated. In one line, X chromosome inactivation has already occurred whereas in the other, X inactivation appears to have been arrested at an intermediate stage. There is reason to suspect that it will be possible to culture female teratocarcinoma cells under conditions in which both X chromosomes retain full activity. We wish to establish that such cells do indeed have two active X's and to investigate the inactivation process which occurs when these cells differentiate. For these experiments, we shall make use of the biochemical and genetic procedures which are applicable to tissue culture cell systems.

227. ANALYSIS AND DEFLECTION OF NORMAL DIFFERENTIATION BY USE OF MONOCLONAL ANTIBODIES

Johnson, M. H., Goodall, H., McIlhinney, G., Bighouse, K., University of Cambridge, Dept. of Anatomy, *Hills Rd., Cambridge CB2 1QT, England, United Kingdom*

OBJECTIVE: To investigate the capacity of monoclonal antibodies to various antigens on murine teratocarcinoma cells to react with early mouse embryos, and to modify their development in culture in vitro.

APPROACH: Generate monoclonal antibodies, assay against a panel of cell lines, test for reactivity against embryos by cytotoxicity and immunofluorescence, test effect of culture of embryos in antibody.

228. EXTRACELLULAR MATRIX AND CELL SURFACE IN TERATOCARCINOMA DIFFERENTIATION

Leivo, I., Vaheri, A., Virtanen, I., Wartiovaara, J., Helsingin Yliopisto, Depts. of Electron Microscopy/Pathology, *Fabianinkatu 33, SF00290 Helsinki, Finland*

OBJECTIVES: Characterize changes which occur in extracellular matrix and cell surface during teratocarcinoma differentiation, and understand the significance of these elements in differentiation.

APPROACH: Immunoelectron microscopy, fluorescence microscopy, lectin probes, histoenzymology, biochemical characterization.

PROGRESS: Projects completed: Fibronectin glycoprotein as a marker of teratocarcinoma differentiation. In preparation: Appearance of extracellular matrix material during endodermal differentiation of teratocarcinoma cultures.

229. CONTROL OF DIFFERENTIATION OF TERATOCARCINOMA CELLS IN CULTURE

McBurney, M. W., University of Ottawa, Dept. of Biology, *30 Somerset St. E., Ottawa, Ontario*, K1N 6N5, Canada

OBJECTIVES: When cultured under the appropriate conditions, malignant murine teratocarcinoma cells differentiate to give rise to a variety of simple tissue types, all of which are benign. Most of this project has to do with attempts to investigate this differentiation process with a view to understanding the developmental events which determine the fate of cell clones.

APPROACH: We intend to assess quantitatively the distribution of tissues formed during teratocarcinoma differentiation by means of a battery of assays for tissue-specific substances. Attempts will then be made to perturb the normal developmental program by allowing differentiation to proceed in the presence of certain drugs with known specific sites of action. It may be possible to correlate certain developmental anomalies with certain molecular perturbations and this should give us clues as to where to look for the important events involved with normal cytodifferentiation.

230. DIFFERENTIATION OF TERATOCARCINOMA CELLS

Levine, A. J., Lo, A., Reich, N., Sarnow, P., State University of New York, Health Science Center at Stony Brook, School of Basic Health Sciences, Dept. of Microbiology, *Stony Brook, New York*, 11796, United States of America

Teratocarcinomas from 120 Sv mice produce tumors in isogenic mice but not in BALB/c, C57BL/6 or C3H/He mice. A genetic analysis of tumor rejection indicates that the 129 Av tumors contain two transplantation rejection antigens called ter-1 and ter-2. The 129 Sv tumor expresses the ter-1b and ter-2b allele and the BALB/c mice have ter-1d and ter-2b; the C3H/He mice have ter-1k and ter-2b and the C57BL/6 mice have ter-1b and ter-2x alleles. The d, k and x alleles may be similar or identical. The ter-1 locus maps 8% from H-2 on chromosome 17 on the centromeric or T-locus side of H-2. Experiments are in progress to prepare antisera to these antigens and detect them on the surface cells in culture.

231. CELL INTERACTIONS IN TETRATOCARCINOMA DIFFERENTIATION

Rosenstraus, M. J., Rutgers, the State University of New Jersey, New Brunswick Campus, Douglass College, Dept. of Biological Sciences, *New Brunswick, New Jersey*, 08903, United States of America

The role of cell position and cell interactions in early mammalian embryogenesis will be studied in vitro, using clonal murine embryonal carcinoma (EC) cell lines as a model system. A hypothesis for the initial differentiation event, the formation of a 'rind' of endoderm on the outside of an EC cell aggregate, will be revealed by mixing experiments involving pluripotent and variant nullipotent (unable to differentiate) EC cells. Nullipotent (F-9 or Nulli-SSC1) and pluripotent (PSA-1) EC cells will be mixed to construct aggregates with specific geometries.

The developmental fate (endoderm, mesoderm, ectoderm, EC or death) of the two cell types will be followed by autoradiography in histological sections. To accomplish this, subclones of pluripotent and nullipotent cells that differ in their ability to incorporate 3H hypoxanthine will be used. These studies will test the hypothesis that cells must be located on the outside of an aggregate in order to differentiate into endoderm. The hypothesis suggested by the first set of experiments can be further tested by similar experiments in which endodermal cells are aggregated with pluripotent and nullipotent EC cells. For future research aimed at detailing the steps in the differentiation pathway, developmental mutants of pluripotent EC cells will be isolated. These studies will help to define the mechanisms that lead to the differentiation and, consequently, the reversion of the malignant phenotype of EC cells.

232. ROLE OF HORMONES, CALCIUM, AND CYCLIC NUCLEOTIDES IN MEDIATING CELL DIFFERENTIATION

Anderson, W. B., Nagarajan, L., Evain, D., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

Studies have concerned the regulation of hormonal responsiveness of embryonal carcinoma (EC) cells versus differentiated cell types and the role these changes in hormonal responsiveness might play in regulating differentiation. Initial studies have dealt with the characterization of the adenylate cyclase system of EC cells and F9 cells, a teratocarcinoma cell line that undergoes limited differentiation under normal culture conditions. Of particular interest is the finding that these embryonic cells are quite responsive to calcitonin; this hormonal response is apparently developed just prior to differentiation into endodermal cell types. This raises the possibility that cells develop a calcitonin-sensitive cyclase system to modulate cyclic AMP and calcium levels and in this manner regulate specific cellular processes during development. Other studies have established that F9 cells can be grown under defined, serum-free conditions in the presence of the somatomedin-like peptide MSA, transferrin, and fibronectin. This system should prove useful to study the alteration of responsiveness to, and the mechanism of action of, insulin-like mitogenic factors.

233. CONTROLLED DIFFERENTIATION OF TEROTOMA CELLS

Carr, B. I., University of Wisconsin, Madison Campus, Center for the Health Sciences, *500 Lincoln Dr., Madison, Wisconsin,* 53706, United States of America

This is part of a broader project. A summary of this subproject is not available.

234. USES OF TERATOCARCINOMA STEM CELLS AS AN ALTERNATIVE TO THE NORMAL EMBRYO

Martin, G. R., University of California, San Francisco Campus, School of Medicine, Dept. of Anatomy, *551 Parnassus Ave., San Francisco, California,* 94122, United States of America

The proposed research involves studies of embryonal carcinoma cells, which are the stem cells of teratocarcinomas. These cells are pluripotent, that is they can form derivatives of all three primary embryonic germ layers. Certain mouse teratocarcinoma stem cell lines are capable of differentiation in vitro, in a manner which parallels normal embryogenesis. The major objective of the proposed research is to use such cell lines to gain new information about the processes of cellular determination and differentiation. In particular, we will study the process of endoderm formation by pluripotent embryonal carcinoma cells, and phenomenon of X-chromosome inactivation in vitro. Experiments will be performed using those cell lines which are already available, and new teratocarcinoma stem cell lines will also be isolated from tumors in a variety of murine inbred strains and from human teratoma tumors. We hope to obtain some euploid murine embryonal carcinoma cells lines which will then be used for blastocyst injections to generate new lines of mice and eventually to generate animal models for human genetic diseases. The obtained results should help us to gain a better understanding of the process of embryonic development as well as to elucidate the nature of the malignant stem cells and the factors which influence their ability to behave as normal embryo cells.

235. DIFFERENTIATION OF ENDODERM FROM TERATOCARCINOMA CELLS

Grainger, J. L., University of California, San Francisco Campus, Cancer Research Inst., Dept. of Anatomy, *551 Parnassus Ave., San Francisco, California,* 94122, United States of America

Under the appropriate culture conditions, embryonal carcinoma cells differentiate into embyroid bodies, structures containing an inner core of undifferentiated stem cells surrounded by a layer of endoderm. These structures are analogous to the inner cell mass of early pre-implantation embryos. Three cell lines have been isolated that differ in the type and quantity of endodermal derivatives that form after the initial aggregation of embryonal stem cell. Using these cell lines and antibodies to a cell-specific marker CH1-fetoprotein, for visceral endoderm, or Reichert's membrane, for parietal endoderm, I plan to study the control of the differentiation of visceral and parietal endoderm under conditions that closely mimic the blastocoelic environment of the normal mouse embryo. By manipulating the ionic concentrations and the pH of the medium, it should be possible to study the control of the differentiation of endoderm as well as other terminally differentiated cell types.

236. CELL INTERACTIONS IN TERATOCARCINOMA DIFFERENTIATION

Rosenstraus, M. J., Rutgers, the State University of New Jersey, New Brunswick Campus, Douglass College, Dept. of Biological Sciences, *New Brunswick, New Jersey,* 08903, United States of America

The role of cell position and cell interactions in early mammalian embryogenesis will be studied in vitro, using clonal murine embryonal carcinoma (EC) cell lines as a model system. A hypothesis for the initial differentiation event, the formation of a 'rind' of endoderm on the outside of an EC cell aggregate, will be revealed by mixing experiments involving pluripotent and variant nullipotent (unable to differentiate) EC cells. Nullipotent (F-9 or Nulli-SSC1) and pluripotent (PSA-1) EC cells will be mixed to construct aggregates with specific geometries. The developmental fate (endoderm, mesoderm, ectoderm, EC or death) of the two cell types will be followed by autoradiography in histological sections. To accomplish this, subclones of pluripotent and nullipotent cells that differ in their ability to incorporate 3H hypoxanthine will be used. These studies will test the hypothesis that cells must be located on the outside of an aggregate in order to differentiate into endoderm. The hypothesis suggested by the first set of experiments can be further tested by similar experiments in which endodermal cells are aggregated with pluripotent and nullipotent EC cells. For future research aimed at detailing the steps in the differentiation pathway, developmental mutants of pluripotent EC cells will be isolated. These studies will help to define the mechanisms that lead to the differentiation and, consequently, the reversion of the malignant phenotype of EC cells.

237. DIFFERENTIATION OF TERATOCARCINOMA CELLS

Levine, A. J., Sekikawa, K., Sarnoff, P., Balint, R., Princeton University, Graduate School, Dept. of Biochemical Sciences, *205 Nassau Hall, Princeton, New Jersey,* 08540, United States of America

Teratocarcinomas are tumors composed of many differentiated tissue types derived from a pluripotential stem cell called embryonal carcinoma cells (EC cells). This proposal details three different experimental approaches to investigate the events occurring during the commitment of EC cells to differentiate. 1) The commitment to extensive differentiation of EC cells in vitro requires first the aggregation of these cells and second the attachment of the aggregates to the surface of the culture dish. If a nullipotent EC cell line which cannot differentiate in vitro or in vivo, forms a mixed aggregate with a pluripotent cell line (which can differentiate), then extensive diferentiation is prevented with only endoderm being formed. This endoderm is formed exclusively from the pluripotential cell type, which in a mixed aggregate is lost (differentiates) at a rate 10 times faster than these same cells are in pure pluripotential aggregates. Thus the nullipotential cells in a mixed aggregate exert an effect upon the pluripotential EC cells. Experiments are proposed to examine the role of cell sorting and cell position in mixed aggregates and its effect upon the ability of EC cells to differentiate. Cell surface antigens of EC cells will be detected by the use of monoclonal antibody which prevents aggregation or development in vitro. 2) Somatic cell hybrids between pluripotential and nullipotential cell lines produce many differentiated tissue types in vivo. Nullipotential x nullipotential hybrids made from the same parent cell line (homozygous) fail to differentiate. Nullipotential x nullipotential hybrids from two different (independently derived) cell lines do differentiate in vivo. Experiments are proposed to carry out a large number of nulli x nullipotential hybrid crosses (complementation matrix) to determine the number of functionally different ways a pluripotential cell may become nullipotential. 3) A teratocarcinoma transplantation rejection antigen has been identified and genetically mapped to chromosome 17 (8.8% recombination units from H-2) in the mouse. Experiments are proposed to develop the appropriate congenic strains of mice, genetically map other such antigens and analyse their effect upon spontaneous teratocarcinomas of the 129 mouse.

238. EGF AND ITS RECEPTORS IN EMBRYONIC DIFFERENTIATION

Adamson, E., Schwartz, C., La Jolla Cancer Research Foundation, *417 Coast Blvd. S., Box 1376, La Jolla, California*, 92037, United States of America

The role of epidermal growth factor (EGF) and its receptors (EGF-R) during embryonic development and during the differentiation and loss of tumorigenicity of teratocarcinoma cells will be studied.

Epidermal growth factor receptors have been demonstrated on the cell surface of certain differentiated teratocarcinoma cell lines. Undifferentiated embryonal carcinoma (EC) cells are malignant and totipotent, but their differentiated cell products have little or no tumorigenicity. The former cells do not have significant numbers of 125I-EGF binding sites and the hypothesis is that in the teratocarcinoma system, growth control may be governed by EGF and its receptors (EGF-R). In many respects, teratocarcinoma cells are a model of mouse development, and this suggests that the tissues of the mouse may become subject to growth control during development either by a) the appearance of EGF-R and maternal EGF or by b) the synthesis of EGF as well as EGF-R. Other markers of endoderm differentiation will be alpha-fetoprotein, transferrin, and basement membrane collagens.

It is intended to study the first appearance and the distribution of EGF-R in mouse embryos using labeled EGF. Further studies of receptor distribution in differentiating EG cells will be made. The binding and molecular characteristics of EGF-R in various cells will be compared to find out if different forms exist. Antibodies to EGF will be prepared and used to study the synthesis of EGF by mouse embryonic tissues and in teratocarcinoma cells by immunological methods. Endogenous growth factors produced by EC cells will be sought. We hope to establish embryonic cell lines using EGF and other factors to stimulate growth.

239. MECHANISMS OF INTERCELLULAR ADHESION

Oppenheimer, S. B., Capelle, C., Sorensen, S., Saxton, W., Ribbons, L., Pearson, L., Schwarzbein, A., Kelley, R., Grade, B., Waian, S., California State University, Northridge Campus, School of Science & Mathematics, Dept. of Biology, *18111 Nordhoff St., Northridge, California*, 91324, United States of America

Cell adhesion is important in developmental events and in tumor spread. The nature of the mechanisms of intercellular adhesion is not well understood. Over the past decade we have contributed to an understanding of this problem by identifying glutamine requiring pathways involved in cell adhesion and by demonstrating that specific carbohydrate groups at the cell surface appear to play a role in the adhesion mechanism. This project extends our studies by (1) examination of the role of specific tumor cell populations in production and binding of teratoma adhesion factor; (2) preliminary characterization of teratoma adhesion factor; (3) isolation of teratoma adhesion factor cell surface receptor sites; (4) identification of terminal carbohydrates involved in cultured teratoma cell adhesion. We hope that our multi-faceted approach to the problem of cell adhesion will result in a better understanding of the molecular basis for adhesion and of the reasons for the altered adhesiveness of malignant tumor cells.

240. CELL SURFACE ANTIGENS OF TRANSFORMED CELLS - TERATOMAS

Levine, A. J., State University of New York, Health Science Center at Stony Brook, School of Basic Health Sciences, Dept. of Microbiology, *Stony Brook, New York*, 11790, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

241. MOUSE TERATOCARCINOMA - A SYSTEM TO STUDY MAMMALIAN DIFFERENTIATION AND NEOPLASIA

Illmensee, K., Duboule, D., Illmensee, R., Petzoldt, U., Universite de Geneve, Lab. of Cell Differentiation, Dept. of Animal Biology, *154 Rte. de Malagnou, CH1224 Geneva, Switzerland*

OBJECTIVE: To study xenogeneic gene expression and the developmental potential of malignant hybrid cells in chimeric mice.

APPROACH: Malignant hybrid cells of rat hepatoma x mouse teratocarcinoma origin were injected into C57BL/6 mouse blastocysts which subsequently were transferred into the uteri of pseudopregnant ICR females. Fetuses at days 15-18 were autopsied and analyzed for hybrid cell derived tissue contributions. In all four chimeric fetuses the hybrid cell participated in liver differentiation and also contributed to a limited number of organs of endomesoderm origin. The presence of rat chromosomes was confirmed by karyotypic analysis of the chimeric organs. Rat gene expression in these chimeric tissues was demonstrated by the presence of rat-specific enzyme variants and proteins, revealed by use of acetate and 2-D gel electrophoresis. The appearance in vivo of certain rat-specific gene products that were not found in the hybrid cells under conditions in vitro as well as tissue-specific modulation of enzyme patterns documented functional gene expression of the introduced xenogeneic chromosomes. After subcutaneous injection of these chimeric tissues into nude mice about one third of them developed tumors with a cellular and biochemical phenotype similar to, but not identical with, the hybrid cell tumors. These results indicate that rat x mouse hybrid cells are capable of participating in organ differentiation but also retain their malignant properties to some extent.

(This research is carried out in collaboration with Dr. C. Croce, Wistar Institute, Philadelphia, PA 19104, USA.)

242. DIFFERENTIATION IN EARLY MOUSE EMBRYO AND TERATOCARCINOMA (HUMAN, MICE)

Solter, D., Wistar Inst. of Anatomy & Biology, *36th & Spruce Sts., Philadelphia, Pennsylvania*, 19104, United States of America

This is part of a broader project. A summary of this subproject is not available.

243. MOUSE TERATOMA AND DERIVED CELLS STUDIES

Chung, A. E., Braginski, J. E., Madhav, R., Lewis, M., University of Pittsburgh, School of Arts & Sciences, Dept. of Biological Sciences, *4200 5th Ave., Pittsburgh, Pennsylvania*, 15260, United States of America

The long-term objective of this project is to study the mechanism of differentiation of mouse embryonal carcinoma cells. The clonal cell lines PCC4-F, PCC4-aza-1, and PCao will be used for these studies. Emphasis will be placed on the in vitro differentiation of these cell lines. The specific approaches will be: (1) Examination of the influence of embryonal carcinoma cell cytoplasm on the gene expression in differentiated cells and the influence of the cytoplasm of differentiated cells on the multipotentiality of embryonal carcinoma cells. (2) comparison of the properties of the embryonal carcinoma cell with embryonal carcinoma derived lines PFHR-9 and M1536-B3. (3) development of an in vitro myogenic differentiation pathway and (4) exploration of the effect of a limited number of extrinsic factors on the differentiation of the embryonal carcinoma cell.

BIBLIOGRAPHIC REFERENCES: Properties of a Basement Membrane Related Glycoprotein Synthesized in Culture by a Mouse Embryonal Carcinoma Derived Cell Line. Albert E. Chung, Ronald Jaffe, Ian L. Freeman, Jean-Paul Vergnes, Janina E. Braginski, and Barry Carlin. Cell, 16, 227-287 (1979).

244. DIFFERENTIATION OF MURINE TERATOCARCINOMA CELLS PERMITS SV40 GENE EXPRESSION

Segal, S., Khoury, G., May, E., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Virus Tumor Biology Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

Infection of differentiated mouse embryo cells by simian virus 40 (SV40) leads to the production of the early mRNAs and the tumor (T) antigens that they encode. In contrast, undifferentiated F-9 murine teratocarcinoma cells do not support these early stages of the SV40 cycle. This block results, at least in part, from the inability to accumulate stable processed early SV40 mRNAs. It has recently been shown that vitamin A and its derivatives can induce in vitro differentiation of stem cells. Undifferentiated F-9 cells, upon treatment with a low concentration of retinoic acid, exhibited pronounced morphologic changes as well as the appearance of the H-2 surface antigens. After differentiation, the susceptibility of F-9 cells to SV40 infection could be demonstrated by the appearance of large T- and small t-antigens, as shown by immunofluorescence and immunoprecipitation. Furthermore, S1 nuclease mapping of early SV40 transcript confirmed the presence of the two spliced early mRNAs. These results indicate that the undifferentiated F-9 stem cells contain the genetic information needed for generating stable processed early SV40 mRNAs but are blocked in the production of functional species.

BIBLIOGRAPHIC REFERENCES: Segal, S., Levine, A.J., and Khoury, G.: Evidence for nonspliced SV40 mRNA in undifferentiated murine teratocarcinoma cells. Nature, 280-335-337, 1979. Segal, S., and Khoury, G.: The regulation of SV40 Gene Expression in Non-permissive Cells. ICN-UCLA, 1980, in press.

C. GENETIC STUDIES OF TERATOCARCINOMAS

245. SUSCEPTIBILITY OF MOUSE EMBRYOS AND TERATOCARCINOMA CELLS TO AGENTS WHICH DAMAGE DNA

MacQueen, H., Tate, J., Imperial Cancer Research Fund, Cell Biology Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

During the course of the experiments, it was found that the embryos were highly sensitive to irradiation by the incorporated 35S, being killed by exposure to a dose of 0.05 microcurie/ml (MacQueen, Journal of Embryology and Experimental Morphology, 1979, 52, 203). These experiments also revealed that a line of pluripotent teratocarcinoma cells, A6 (which in certain respects resemble embryonic cells), is more radiosensitive than an aneuploid fibroblast line. We are currently extending these studies to examine the sensitiviry of A6 and a line of diploid mouse fibroblasts (WME) to N-methylN'-nitrosoguanidine, an alkylating agent, and to ultraviolet light. Preliminary results indicate that A6 cells are less able to survive damage caused by these agents than WME cells. This could be due to deficiencies in DNA repair processes in the teratocarcinoma cells, which have been shown previously to have a low rate of sister-chromatid exchange (F. Kelly, personal communication). Study of such repair-deficient cells may provide an insight into ways in which normal cells cope with carcinogen-induced damage to their DNA.

246. INVESTIGATION OF THE GENETICS OF AMINO ACID METABOLISM AND MEMBRANE STRUCTURE AND FUNCTION IN CULTURED MAMMALIAN CELLS

Pateman, J. A., Buultjens, T. E., Carritt, B., MacDonald, C. M., Subak Sharpe, J. H., University of Glasgow, Inst. of Genetics, *Church St., Glasgow G11 5JS, Scotland, United Kingdom*

OBJECTIVE: Genetic analysis of arginine metabolism.

APPROACH: Techniques are being developed for the isolation of mutants of cultured mammalian cells and their subsequent genetic and biochemical analysis. Present approaches concentrate on the isolation of cells resistant to toxic analogues of arginine, and of those displaying a growth requirement for arginine.

The technique of interspecies cell fusion is being used to assign genes involved in arginine metabolism to human chromosomes and to specific subregions of them.

PROGRESS: Mouse teratocarcinoma cells resistant to the toxic arginine analogue canavanine have been obtained. These show a reduced incorporation of radiolabelled arginine into protein, the basis of which is under investigation.

The human gene for argininosuccinate synthetase has been assigned to chromosome 9 (Exp. Cell Res., 106, 71 (1977)). Using translocation mapping it has been further localized to the distal one-fifth of the long arm of this chromosome.

247. DEVELOPMENTAL AND MALIGNANT PROPERTIES OF TERATOCARCINOMA CELL HYBRIDS

McBurney, M. W., University of Ottawa, Dept. of Biology, *30 Somerset St. E., Ottawa, Ontario*, K1N 6N5, Canada

This project represents an approach to investigate the intracellular processes involved in the differentiation of murine embryonal carcinoma cells, the stem cells of teratocarcinomas. The embryonal carcinoma cells are developmentally multipotent and malignant whereas their differentiated progeny are benign.

The approach is to make use of embryonal carcinoma cell cultures and to apply to this system some of the techniques currently available for the genetic manipulation of cells in culture.

Cell hybrids have been isolated following fusion of embryonal carcinoma cells to committed erythroid cells. These hybrids resemble their erythroid parent in their ability to synthesize hemoglobin. I intend to continue investigation of these hybrids to determine the status of the globin genes derived from the embryonal carcinoma parent.

248. ASSESSMENT OF TERATOGENIC AND TOXIC PROPERTIES OF PRODUCTS AND BY-PRODUCTS OF OIL SHALE TECHNOLOGIES

Swartzendruber, D. E., U.S. Dept. of Energy, Los Alamos Scientific Lab., *P.O. Box 1663, Los Alamos, New Mexico*, 87544, United States of America

The objective of this project is to provide a simple diagnostic system using totipotential cells for screening and evaluating energy-related products and by-products for their toxic and/or teratogenic effects on embryonic development. Intrauterine embryonic cells are not practical for large-scale screening of potentially hazardous agents since such systems are hampered by complex, lengthy, and costly techniques and by a paucity of embryonic material. As an alternative to embryos, totipotential stem cells derived from a murine teratocarcinoma (which is analogous to cells of the early mouse embryo) will be used to screen for toxic and/or teratogenic agents. Flow cytometry will be used to quantitate parameters of the in vitro differentiation of teratocarcinoma cells and to detect disruption of these parameters by various agents. Initial characterization of this system by flow cytometry is presently being pursued.

BIBLIOGRAPHIC REFERENCES: D.E. Swartzendruber, B.J. Price and L.B. Rall, Multiangle Light-Scattering Analysis of Murine Teratocarcinoma Cells, J. Histochem. Cytochem., 1978. S.S. Barham, D.E. Swartzendruber and R.A. Walters, Flow Microfluorometric Analysis of Bromodeoxyuridine-Mithramycin Treated Cells After X-Irradiation, Radiat. Res., 1978.

249. MOUSE TERATOCARCINOMA, MAMMALIAN DIFFERENTIATION AND DISEASE

Illmensee, K., Bluthmann, H., Burki, K., Petzoldt, U., Universite de Geneve, Dept. of Biology, *Rue de Candolle 3, 1211 Geneva 4, Switzerland*

OBJECTIVE: The aims of our program are to cycle malignant cells through mice to identify the developmental basis of genetic defects or neoplasia and to gain insight into the mechanisms controlling gene activity during mammalian differentiation. Specific emphasis is focused on the in vivo potential and the reversibility versus stability of malignancy of various cancer cells.

APPROACH: Malignant cells from various mouse teratocarcinomas, human x mouse or rat x mouse hybrid cell lines are injected into mouse blastocysts carrying several genetic markers. After micromanipulation, the blastocysts are surgically implanted into the uterus of pseudopregnant foster mothers to allow development to term. The live-born mice are analyzed for tumor cell-derived contributions in the coat, internal organs, and germ line using enzyme electrophoresis, histochemical and histological techniques, and breeding tests.

PROGRESS: Hybrid cells between mouse teratocarcinoma, deficient in thymidine kinase, and human fibrosarcoma or rat hepatoma, deficient in hypoxanthine phosphoribosyltransferase, lost their malignant properties after microinjection into C57BL/6 blastocysts and contributed normally in differentiation of several adult tissues. Human-specific galactokinase could be detected in two different organs of two chimeric mice. Nine rat-specific enzymes were present in a limited number of tissues of three chimeric mice. The in vivo appearance of certain rat gene products, usually not found in the hybrid cells in vitro, documented functional expression of the xenogeneic genes.

250. GENE EXPRESSION DURING MAMMALIAN DEVELOPMENT

Illmensee, K., Croce, C. M., Bluthmann, H., Universite de Geneve, *Rue de Candolle 3, 1211 Geneva 4, Switzerland*

The aims of our program are to cycle hybrid cells between mouse tetratocarcinoma cells and various kinds of differentiated rodent and human cell lines through mice via blastocyst injection in order to trace histochemically their cell lineage and to study the mechanisms controlling gene activity during mammalian development. The in vitro system of genes, chromosome fragments and entire chromosomes integrating into teratocarcinoma cells, in combination with the bioassay of introducing these hybrid cells into the living organism, allows us to assay for the appearance, coexistence, and regulation of the foreign gene products in the different organs of chimeric mice. We aim to establish (1) whether it is possible to channel the differentiation of the hybrid cells into specific tissues, (2) whether nuclear or cytoplasmic factors derived from the parental differentiated cells are responsible for the tissue preference of the hybrid cells, and (3) what specific chromosomes are responsible for this phenomenon. We have introduced the gene for mouse lambda immunoglobulin chain into the pBR322 plasmid EcoRI site of our pHSV106 vector containing the 3.4 Kb Bam H1 DNA fragment containing the herpes simplex virus type 1 thymidine kinase gene. We intend to transform thymidine kinase deficient mouse teratocarcinoma cells with such recombinant DNA molecules and inject the transformants into mouse blastocysts in order to examine the chimeric tissues for the expression of the already rearranged lambda chain DNA sequences. If the exogenously introduced lambda chain gene is expressed in B cells we will introduce deletions and insertions in flanking, coding and intervening DNA sequences of the lambda chain DNA and repeat the transformation experiments. Injection of cloned mouse lambda immunoglobulin chain DNA with and without vector into fertilized mouse eggs should facilitate its chromosoamal integration and transmission through the germ line of the host organism. This novel approach will allow us to correlate the molecular structure of defined hereditary elements with its developmental phenotype.

251. TERATOCARCINOMA HOST RANGE RESTRICTION OF SV40

Levine, A. J., Kuehn, D. J., State University of New York, Health Science Center at Stony Brook, School of Basic Health Sciences, Dept. of Microbiology, *Stony Brook, New York*, 11790, United States of America

SV40 can infect murine teratocarcinoma cells in culture. The virus absorbs, penetrates and synthesizes virus specific RNA. This RNA is not however processed properly in these cells and no viral early proteins are detected. Murine cells differentiated from the stem cells of teratocarcinomas do express SV40 early viral proteins and can be transformed by this virus. Thus the expression of SV40 early proteins in a differentiating murine teratocarcinoma cell system becomes an assay for the acquisition of RNA processing activities.

Using the assay, the kinetics of appearence of these RNA processing activities during differentiation in vitro will be followed. Both immunoprecipitation of labeled protein and fluorescent antibody techniques will be employed to 1) localize the cell type and 2) analyze the structure of the SV40 early proteins. Somatic cell hybrids will be constructed to determine the dominance relationships between embryonal carcinoma cells and differentiated cells. Both mouse-mouse and mouse-human hybrids will be analyzed. In this way the regulation of RNA processing activities with the differentiated state can be followed.

252. TERATOCARCINOMA - VIRUSES AND DIFFERENTIATION

Lehman, J. M., Pierce, G. B., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Pathology, *4200 E. 9th Ave., Denver, Colorado*, 80262, United States of America

A teratocarcinoma is a highly malignant tumor of germ cell origin which contains tissues from all three germ layers (ectoderm, mesoderm and endoderm) and embryonal carcinoma. An embryonal carcinoma, the stem cell of the murine teratocarcinoma, has been established as cell lines. These cells have retained the ability to produce teratocarcinomas when injected into animals, and the potential to differentiate into various cells and tissue types in vitro. Thus, this system is unique for study of the process of neoplastic differentiation and effects of various agents (i.e. viruses) on this process.

Simian virus 40 and polyoma viruses are capable of infecting the differentiated progeny of embryonal carcinoma, but are not able to infect the embryonal carcinoma cells. Therefore, the response to infecting viruses may be controlled by the state of differentiation of the host cells. The mechanism of this differential response utilizing SV40, polyoma virus, and an RNA virus, Mengo virus, is under study.

253. GENE EXPRESSION IN TERATOCARCINOMA CELLS

Linney, E. A., La Jolla Cancer Research Foundation, *417 Coast Blvd. S., Box 1376, La Jolla, California*, 92037, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

254. TERATOCARCINOMA CELLS AS A MODEL SYSTEM FOR X-CHROMOSOME INACTIVATION

Donoghue, D. J., University of California, San Francisco Campus, Cancer Research Inst. Dept. of Anatomy, *551 Parnassus Ave., San Francisco, California*, 94122, United States of America

This proposal involves the use of teratocarcinoma stem cells as a model system for studying X-chromosome inactivation. Teratocarcinoma stem cells are pluripotent and closely resemble cells of preimplantation embryos. Recently, a teratocarcinoma stem cell line containing two active X-chromosomes was isolated; by altering the culture conditions, these cells could be induced to undergo X-chromosome inactivation in vitro.

The first goal will be to isolate a teratocarcinoma cell line heterozygous for X-linked markers. Using microcell fusion techniques, an active X-chromosome from Mus caroli cells will be introduced into XO HPRT-deficient teratocarcinoma stem cells from Mus musculus. M. caroli and M. musculus differ electrophoretically in many X-linked activities. HAT selection and karyotype analysis will be used to identify a recipient M. musculus teratocarcinoma cell carrying the donor M. caroli X-chromosome.

This cell line would facilitate in vitro differentiation experiments which are prohibited by measurements of gene dosage. For example, is a given X-chromosome always inactivated in its entirety, or can states of partial inactivation occur? Is X-inactivation an irreversible event, or can a previously inactivated X-chromosome undergo reactivation?

Finally, these heterozygous cells will be used in blastocyst injection experiments. The presence of the M. caroli X-chromosome should facilitate incorporation of the teratocarcinoma stem cells into chimeric mice. Hopefully, female mice will be obtained which exhibit germ-line chimerism. The introduction of the X-chromosome of M. caroli into the laboratory strain of mice, and the resultant heterozygosity of X-linked enzymes, would prove an invaluable tool for studying X-inactivation in the embryo.

255. REGULATION OF FOREIGN GENES IN TERATOCARCINOMA CELLS

Efstratiadis, A., Lo, C. W., Harvard University, Boston Campus, School of Medicine, Dept. of Biological Chemistry, *25 Shattuck St., Boston, Massachusetts*, 02115, United States of America

The overall objective of this project is to study the role of specific DNA sequences of well characterized eukaryotic genes in the regulation of expression of those genes in mouse teratocarcinoma stem cells as a function of differentiation.

Unmodified cloned insect chorion chromosomal DNA and rabbit beta-globin chromosomal DNA will be ligated to the herpes simplex viral DNA fragment coding for the enzyme thymidine kinase (TK). This hybrid DNA molecule will be used to transform teratocarcinoma stem cells which are TK deficient (TK negative). Cells which have incorporated this hybrid DNA will express TK activity and survive selection in (HAT medium) medium which is cytotoxic to TK negative cells. The expression of the corresponding mRNA and protein of the chorion and beta-globin genes in these transformed teratocarcinoma cells will be analyzed before and after their differentiation in vitro and as a tumor in vivo. In parallel to these experiments, specific structural modifications, including the removal of intervening and flanking sequences, will be introduced in the chorion and beta-globin gene prior to its ligation to form the hybrid molecule. Once again similarly transformed cells will be analyzed for expression of the chorion and beta-globin genes before and after cell differentiation.

Thus it is hoped that such an approach may provide clues to the possible involvement of specific DNA sequences within a gene in the regulation of gene expression and the relationship of this control to the regulation of differentiation and cell determination.

256. X-CHROMOSOME ACTIVITY IN TERATOCARCINOMA STEM CELLS

Martin, G. R., Takagi, N., Donoghue, D. J., University of California, San Francisco Campus, School of Medicine, Dept. of Anatomy, *551 Parnassus Ave., San Francisco, California,* 94122, United States of America

The objective of this work is to study the phenomenon of X-chromosome inactivation or gene dosage compensation using malignant teratocarcinoma stem cells. Our previous studies indicated that certain pseudo-diploid XX-teratocarcinoma stem cell lines contain two genetically active X-chromosomes as long as they are maintained in the undifferentiated state, and that the cells can undergo X-inactivation when they are allowed to differentiate in vitro. We propose here to further explore the extent to which such tumor stem cells can provide a valid model system for the study of X-inactivation. To do this, we will isolate new teratocarcinoma stem cell lines by a variety of techniques, including interspecies microcell fusion, to obtain cells that are heterozygous for electrophoretic variants of X-linked enzymes. The availablilty of such cell lines will enable us to confirm by enzyme gel electrophoresis our earlier conclusions. In other experiments we will study the cytogenetic properties of the X-chromosomes in the cells to determine the temporal relationship between the onset of cytological manifestations of X-inactivation (e.g., late replication of DNA) and of biochemical inactivation. In addition, we will determine whether an inactive X-chromosome can be reactivated by placing it in a teratocarcinoma stem cell. Also, when appropiate interspecies hybrid cell lines are available we plan to carry out blastocyst injections in order to obtain chimeric mice. If the injected cells form functional germ cells in these mice we will have thus created a new line of mice that cary an X-chromosome that expresses X-linked gene products with electrophoretic mobilities different from those which are common in laboratory mice. Such mice will be an invaluable tool in studies of X-chromosome activity during normal embryonic development. The results of the studies described here should lead to a better understanding of the X-inactivation process during normal early embryogenesis and may help to explain gene regulation throughout normal development.

257. GENE CONTROL OF MAMMALIAN DEVELOPMENT AND DISEASE

Mintz, B., Fleischman, R. A., Wagner, E., Stewart, T. A., Karin, M., Inst. for Cancer Research, *7701 Burholme Ave., Philadelphia, Pennsylvania,* 19111, United States of America

The chief objectives of the program are to analyze genetic and epigenetic mechanisms in mammalian differentiation, genetic diseases, and malignancy. Several experimental systems are being utilized. One of these depends upon the capacity of mouse teratocarcinoma stem cells to lose their malignancy and participate in development when microinjected into early-stage mouse embryos. In the best cases, germinal derivatives are formed; thus, progeny with the tumor-lineage genes are obtained. The tumor stem cells may therefore serve as vehicles for introducing into mice predetermined mutations, including some designed to yield laboratory models of human genetic diseases: Teratocarcinoma cells, after mutagenesis during in vitro culture, are selected or screened to obtain clones with the desired mutation, and the mutant cells are then injected into embryos. In another approach, recombinant cloned genes are being introduced either into the teratocarcinoma cells or directly into embryos, in order to analyze the relationship between gene organization and tissue-specific control of gene expression. An additional experimental system has recently been devised here for investigating genetic and developmental mechanisms involved in hematopoiesis: This depends upon early prenatal substitution of the hematopoietic cell lineage with genetically marked hematopoietic stem cells.

BIBLIOGRAPHIC REFERENCES: Mintz, B. (1979). Teratocarcinoma cells as probes of mammalian differentiation. In: Mechanisms of Cell Change (J. Ebert and T. Okada, eds.), 119-127. John Wiley and Sons, Inc., New York. Mintz, B. (1979). Teratocarcinoma cells as vehicles for introducing mutant genes into mice. Differentiation 13, 25-27.

258. SELECTION OF DRUG RESISTANT MUTANTS OF MOUSE AND HUMAN TERATOCARCINOMA CELLS

Croce, C. M., Wistar Inst. of Anatomy & Biology, *36th & Spruce Sts., Philadelphia, Pennsylvania,* 19104, United States of America

This is part of a broader project. A summary of this subproject is not available.

259. MECHANISMS OF OVARIAN TERATOCARCINOGENESIS

Eppig, J. J., Jackson Lab., *Box 258, Bar Harbor, Maine,* 04609, United States of America

Fifty percent of strain LT/Sv female mice have ovarian teratomas by the time they are three months old. Ovarian teratomas in mice and humans are derived from oocytes that complete the first meiotic division and develop parthenogenetically within the ovaries. Therefore, in order to understand the mechanisms of ovarian teratocarcinogenesis it is critical to know the factors that promote parthenogenetic activation and the conditions of meiotic maturation that promote the subsequent embryonic development of parthenotes. The first set of experiments proposed here focuses on the hormonal and genetic factors involved in the development of the ability of strain LT/Sv oocytes to become spontaneously parthenogenetically activated after meiotic maturation. The second set of proposed experiments focuses on the requirements for serum and cumulus cells during oocyte maturation for the acquisition of parthenogenetic embryological developmental competence to form blastocysts. Emphasis will be placed on the timing crucial for when serum and cumulus cells are necessary during maturation, on the general biochemical characterization of the active serum component(s), and on the nature of the interactions between cumulus cells and oocytes.

A high frequency of ovarian teratocarcinogenesis in mice is correlated with a high frequency of unique granulosa cell deficient (GCD) follicles. Parthenogenetically developing embryos are found in the GCD follicles in LT/Sv mice. A third objective of this proposal is to determine qualitatively whether or not GCD follicles develop atypically in terms of the gonadotropin receptors thought to be critical for normal follicular development.

260. HLA AND GENETIC MARKERS FOR TERATOCARCINOMA

DeWolf, W. C., Yunis, E. J., Bellve, A. R., Sidney Farber Cancer Center Inc., Dept. of Immunogenetics, *44 Binney St., Boston, Massachusetts,* 02115, United States of America

The objective of this proposal is to investigate the significantly increased HLA-Dw7 antigen frequency in patients with testicular teratocarcinoma. This will be done by critically analyzing and reconstructing the triangular relationship between the mouse major histocompatibility complex (H-2), the T/t complex, and teratocarcinoma, and then applying this information, as a guide to look at genetic regions in linkage with HLA in hopes of defining genetic markers in association with teratocarcinoma. Experiments will be designed comparing a testicular teratocarcinoma population to a normal control population from the same geographical area in terms of: 1) Genetic markers in linkage with HLA (GLO, PGM3, Bf, C2 and HLA-DR) and 2) genetic markers expressed on spermatozoa. Because T/t complex alleles are expressed only on spermatozoa as the only normal adult tissue in mice and control the expression of a teratocarcinoma associated antigen on sperm (F9), a systematic investigation will be made for a T/t complex-like region near HLA (in the human), controlling the expression of genetic markers present on spermatozoa of teratocarcinoma patients. Considering the homology between the mouse and human major histocompatibility complex (H-2 and HLA), such a region in the human should be included within the same genetic areas as the other markers, i.e. between HLA-D and the centromere. The detection of spermatozoa-specific teratocarcinoma associated antigens will involve three different techniques: 1) Lymphocyte-spermatozoa primed lymphocyte typing (PLT); 2) two-dimensional protein electrophoresis of various components of spermatozoa and 3) screening of sera (i.e., HLA alloantisera, sera from teratocarcinoma 'patients) for anti-spermatozoa activity. We expect that the structural, genetic, and developmental association between teratocarcinoma, and T/t complex, and H-2 in the mouse, will help unravel the relationship between HLA-Dw7 and teratocarcinoma as well as provide an effort toward the definition of a T/t complex-like region in the human.

261. CYTOGENETICS OF CLONAL NEOPLASIAS

Hecht, F., Peakman, D. C., Kaiser McCaw, B., Cadien, J. D., Villafane, S. E., Southwest Biomedical Research Inst., Cancer Cytogenetics Unit, *123 E. University Dr., Tempe, Arizona*, 85281, United States of America

This research is mainly on culture and cytogenetics of premalignant and malignant cells. The cells are selected from patients with hematologic malignancies such as lymphomas and juvenile myeloid leukemia and with chromosome instability-immunodeficiency diseases such as ataxia-telangiectasia. Key elements in the experimental design include direct chromosome studies, early sampling of cell cultures, repeated longitudinal studies, analysis of relatively large numbers of cells each time, and complete data recording and analysis. Methods include direct chromosome studies, modifications in short- and long-term cell culture, establishment of lymphoma cell lines, cell cloning, lymphoblast culture, sequential chromosome banding, semiautomated densitometry of banded chromosomes, T- and B-cell determination, enzyme electrophoresis and computer recording and data analysis. Ovarian teratomas will be studied for gene-centromere mapping.

Our immediate aims are to collect accurate cytogenetic data from direct preparation and cultured cells. Our long-term aims are to 1) understand clonal evolution, especially of lymphomas; 2) employ cytogenetic and cell origin information in order to diffuse histiocytic and other non-Hodgkin's lymphomas into homogeneous classes; 3) determine interlocking patterns of chromosome change embracing clinically distinct disorders; 4) learn general principles regarding chromosomes in malignancy including clarification of the role of chromosome 14 in lymphoid malignancy and 5) test whether position effect may occur in neoplastic chromosome rearrangements.

262. TERATOCARCINOMA AND ONCO-EMBRYONIC PHENOTYPE

Damjanov, I., Martinez Hernandez, A., Hahnemann Medical College, Dept. of Pathology & Laboratory Medicine, *235 N. 15th St., Philadelphia, Pennsylvania*, 19102, United States of America

The overall objective of this proposal is to study the epigenetic factors that favor, modify or inhibit the expression of the malignant phenotype of undifferentiated embryonic cells and stem cells of teratocarcinoma. In a continuation of our present studies we plan to investigate the differentiation and growth of normal embryonic cells and embryonal carcinoma cells transplanted into adult hosts or injected into developing embryos as well as under controlled conditions in vitro. Differentiation and growth of embryonic cells and embryonal carcinoma cells will be primarily investigated as a function of interaction between the undifferentiated cells and somatic cells in the adult or embryonic cells in utero and in vitro. Chemical and biological approaches to modify the differentiation will be pursued. The genome of the embryonal cells will be manipulated to determine the effects of genomic alterations on expression of malignant phenotype. Differentiation and/or expression of onco-embryonic phenotype will be monitored by light and electron microscopy using enzyme histochemical and immunocytochemical techniques. These studies are intended to increase our understanding of basic mechanisms accounting for the transition of normal embryonic cells into stem cells of teratocarcinoma and the epigenetic control of malignancy in general.

263. TERATOGENIC MECHANISMS AND PRESCREENING SYSTEMS

Russell, L. B., Filler, R. S., U.S. Dept. of Energy, Oak Ridge National Lab., *P.O. Box X, Oak Ridge Operations Office, Oak Ridge, Tennessee*, 37830, United States of America

At present, compounds that are produced in coal-related technologies have unknown teratogenic potential. In coordination with the ORNL Coal Conversion Project, we hope to test such compounds for their capacity to cause abnormal embryonic development. A sensitive and rapid quantitative prescreen has been developed and is being refined to aid in such tests. Teratological pathways are thought to be initiated by differential cell killing or slowing of division rates, by alteration of differential potential of primordial cell types, or by a combination of these factors. Further, in mammals, a teratogenic agent may act not only directly on the embryo itself, but indirectly by exerting an effect on the maternal organism. In order to predict teratogenic potential of chemicals, this project is establishing additional efficient test systems for various aspects of teratogenesis. We are (1) looking for inhibitions of differential capacity of transplantable teratocarcinoma (normally pluripotent), (2) studying reduction in survival after in vivo treatment of early cleavage period embryos, and (3) transplanting treated preimplantation embryos from genetically responsive strains to nonresponsive host females and vice versa. These test systems will not only aid in the detection of potential teratogenic agents but may differentiate factors involved in altering normal developmental patterns.

BIBLIOGRAPHIC REFERENCES: Russell, L.B., Sensitivity Patterns for the Induction of Homeotic Shifts in a Favorable Strain of Mice, Teratology 20: 115-125 (1979). Russell, L.B., Sensitivity of the Homeotic-Shift Prescreen for Environmental Teratogens, Teratology 19: 45A (1979).

V. BIOCHEMISTRY, IMMUNOLOGY, HISTOPATHOLOGY AND CYTOLOGY OF GYNECOLOGICAL CANCERS

A. BIOCHEMICAL STUDIES OF GYNECOLOGICAL CANCERS

264. DETERMINATION OF PROTEASES AND ANTIPROTEASES IN SERUM AND VAGINAL SECRETION OF PATIENTS WITH CERVICOUTERINE CANCER

Benitez Bribiesca, L., Freyre, R., Gallegos, G., Mendoza, M., Alfaro Aceves, L., Hospital de Oncologia, Division de Laboratorios, *Av. Cuauhtemoc 330, Mexico City 7, D.F., Mexico*

OBJECTIVE: To study the presence of proteases and antiproteases at various stages of cervicouterine cancer and determine their relationship to serum levels of the same proteins. In this fashion we will determine whether these proteases and antiproteases occur prior to the elevated serum levels associated with in situ and microinvasive cancer.

APPROACH: We will study 25 women in each of the following 6 groups: cervical carcinoma in situ, invasive carcinoma stages I, II, III, and IV, and acute cervical dysplasia. Two control groups will be comprised of women of comparable age without cancer or dysplasia and of women of comparable age with some form of cancer other than genital.

In all cases we will record age, menstrual cycles, use of hormonal contraceptives, presence of infection or other condition that may affect plasma levels of A-1-AT or proteases. Patients with cervical neoplasia will undergo exfoliative cytologic exam, biopsy, and in some cases conization. Controls will undergo only vaginal cytologic exam without biopsy.

Determinations will include: 1) cathepsin B, 2) trypsinic activity, 3) quantitative A-1-AT and alpha-2-macroglobulin, 4) total serum antiproteolytic activity, 5) total protein, and 6) electrophoresis in agar to observe alpha-1-globulin and A-2-macroglobulin bands.

Results will be tabulated and statistical analyses performed to compare all patient and control groups and obtain t and p values. In this fashion we hope to determine the stage of disease at which the substances under study appear.

265. PROGESTERONE-SPECIFIC PROTEIN IN HUMAN ENDOMETRIAL SECRETIONS

Richardson, G. S., Massachusetts General Hospital, Dept. of Gynecology, *32 Fruit St., Boston, Massachusetts*, 02114, United States of America

The ultimate aim is to determine if malignant endometria produce progesterone-specific proteins that can be detected by radioimmunoassay and provide a diagnostic test for malignant neoplasia or an indicator of the response of a neoplasm to hormonal therapy.

We plan to (a) isolate proteins secreted into the lumen of the uterus during the progestational phase of the menstrual cycle; (b) develop a test for the detection of these materials; (c) determine the influence of steroids on their synthesis; and (d) identify which cell types synthesize them. The secretory proteins isolated from uterine washings will be purified and used as antigens in the rabbit. Antibodies will be used as reagents in immunological assays on biological fluids and tissue sections. Organ and monolayer cell cultures will be used to establish the effect of steroids on the synthesis of these proteins. Once the proteins have been characterized and identified as being progesterone-dependent in normal tissues, washes of cancerous endometria will be examined.

266. PURIFICATION OF CANCER SPECIFIC PEPTIDES FROM URINE

Stenman, U., Helsinki University Central Hospital, Dept. of Obstetrics Gynecology, *Haartman.k. 4, Helsinki, Finland*

OBJECTIVE: To isolate and identify cancer associated peptides, especially from patients with gynecologic cancer, and to set up specific methods for their determination.

APPROACH: Concentration of urine with a new method which allows recovery of peptides with a molecular weight of 1000-10000 (and larger), fractionation of the peptides by gel filtration, and removal of normal peptides and proteins from the fractions by negative affinity chromatography using immunoadsorbents against normal proteins. The fractions thus obtained will be used for immunization. The antisera are tested by crossed immunoelectrophoresis; cancer associated peptides and proteins are purified and used to set up immunochemical determination methods.

PROGRESS: We have prepared antisera and immunoadsorbents against normal urinary protein fractions. Urine from one cancer patient (ovary) has been fractionated and seems to contain at least one abnormal peptide. Final purification and characterization of this peptide is in progress.

267. UTERINE PEROXIDASE AND PEROXIDASE ANTIBODY-REAGENTS FOR STUDY OF ESTROGEN REGULATION OF GENE FUNCTION IN NORMAL AND NEOPLASTIC UTERUS

DeSombre, E. R., University of Chicago, Pritzker School of Medicine, Ben May Laboratory for Cancer Research, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

268. DEVELOPMENTAL ENZYMOLOGY

Chou, J., Mano, T., Schlegel, S., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Inst. of Child Health & Human Development, Pregnancy Research Branch, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

Topics of current interest are: (1) The regulation of the synthesis of placental proteins, alkaline phosphatase and human chorionic gonadotropin in normal placenta, choriocarcinoma and SV40-transformed placental cells. (2) Regulation of differentiated functions (synthesis of alpha-fetoprotein, albumin and transferrin) in liver. (3) Hormonal regulation of glycogenolysis and glyconeogenesis in liver.

BIBLIOGRAPHIC REFERENCES: Sakiyama, T., Robinson, J.C., and Chou, J.Y.: Multiple forms of alkaline phosphatase in untreated and 5-bromo-2'deoxyuridine-treated choriocarcinoma cells. Arch. Biochme. Biophys. 191, 782-791, 1979. Sakiyama, T., Robinson, J.C., and Chou, J.Y.: Characterization of alkaline posphatase from human first-trimester placentas. J. Biol. Chem. 254, 935-938, 1979.

269. MELPHALAN TRANSPORT BY, AND CYTOTOXICITY TO, HUMAN OVARIAN CARCINOMA CELLS

Vistica, D. T., Schuette, B., Torain, B., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Molecular Biology & Methods Development Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

Melphalan uptake by ovarian carcinoma cells isolated from patients with clinically documented disease was reduced 7-fold by incubation of cells with radiolabeled drug in the ascitic fluid when compared to incubation of cells in a balanced salt solution containing albumin and glucose. Automated amino acid analysis of ascitic fluid indicated that it contained physiological concentrations of a number of amino acids, notably leucine (100-150 micromolar) and L-glutamine (500-600 micromolar), which reduce melphalan uptake by ovarian carcinoma cells to levels obtained with ascitic fluid. Cytotoxicity evaluations were in agreement with transport data.

270. CARCINOMA OF OVARY

Norris, H. J., U.S. Dept. of Defense, Armed Forces Inst. of Pathology, *c/o Walter Reed Medical Ctr., Washington, District of Columbia*, 20306, United States of America

An immunohistochemical study of human chorionic gonadotropin (HCG) and alpha-fetoprotein (AFP) in malignant germ cell tumors of the ovary was published in collaboration with the National Cancer Institute in an effort to correlate the type of neoplasm with the presence of markers. The results were published in Ann. Clin. Lab. Sci. 9: 462-466, 1979.

A manuscript has been submitted to Cancer on Sertoli tumors of the ovary. These 29 cases are a special group that have not had ultrastructural features characterized.

Two hundred granulosa tumors have been collected and sent for follow-up in an effort to find out what the prognosis is after ten years of follow-up.

Results of a collaborative epidemiologic study conducted in cooperation with George Washington University was published: McGowen, L., et al. The Women at Risk for Ovarian Cancer. Gynecol. Oncol. 7:325-344, 1979.

A collaborative study with the Gynecologic Oncology Group has led to submission of a paper to Gynecol. Oncology for publication in the near future.

Two book chapters reviewing the AFIP experience with germ cell tumors of the ovary have also been completed. These will appear in Bloodworth's Endocrine Pathology and Copple-son's Textbook of Gynecologic Oncology.

BIBLIOGRAPHIC REFERENCES: Kao, G.F., and Norris, H.J.: Cystadenofibromas with Epithelial Atypia. Amer. J. Surg. Path. 2: 351-363, 1978. Kao, G.F., and Norris, H.J.: Endometrioid, Mucinous and Clear Cell Types. Obstet. Gynecol. 54: 729-736, 1979.

271. CYTOTOXIC FACTOR(S) FROM HUMAN OVARIAN ADENOCARCINOMA

Sheid, B., State University of New York, Downstate Medical Center, School of Medicine, Dept. of Pharmacology, *450 Clarkson Ave., Brooklyn, New York*, 11203, United States of America

Our laboratory has demonstrated the existence of inhibitor(s) of cellular proliferation in the cytosol of human ovarian adenocarcinoma cells, and in the ascites fluid of women with disseminated ovarian cancer. These inhibitory substance(s) are able to inhibit 3H-thymidine uptake by phytohemagglutinin (PHA)-stimulated human lymphocytes and cell growth, in culture, of the murine leukemia L1210. The inhibitor(s) appear to be glycoproteins with molecular weights of 12,000-15,000 daltons. We propose to purify and characterize the physicochemical and biological properties of the inhibitory factor(s). Purification, using cell-free ascites fluid, will be accomplished by employing ultrafiltration membranes, molecular sieve chromatography (Sephadex G-50, hydroxyapatite), ion-exchange chromatography (carboxymethylcellulose, Dowex), and affinity chromatography (a specific lectin covalently bound to Sephadex G-10 or Sepharose). The chemical composition (by various biochemical techniques), molecular weight (by sucrose gradients and gel electrophoresis), sulfhydryl group dependency and cation requirements of the purified inhibitor(s) will be determined. The effect of the inhibitor(s) on target cell DNA, RNA and protein synthesis will also be analyzed. In addition, we will examine the ability of the purified inhibitory material to induce fragmentation of target cell DNA (crude inhibitory extracts appear to function in this manner). Long-term goals are to fully elucidate the chemical structure of the inhibitor(s), to determine their specificity of action by employing various cells lines of lymphoid and nonlymphoid origin, to ascertain their effects on the various components of the cell- and humoral-mediated immune system, and to determine if they have any specific antitumor effects on experimental tumors in vivo.

272. ZINC IN THE HUMAN REPRODUCTIVE TRACT

Whitmore, W., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

273. RNA-DNA RATIOS IN HUMAN OVARIAN TUMORS

deSrulijes, L. K., Barzilai, D., Brandes, J., Dario & Matilde Beraha Center for Hormones in Cancer Res., *Aba Hillel Silver 107/3, Haifa, Israel*

OBJECTIVES: To investigate whether there exists a significant quantitative difference in the RNA:DNA ratio between malignant and benign ovarian tumors and normal human ovaries.

APPROACH: Nucleic acid content in tumors and normal ovarian tissue was determined. Both RNA and DNA were measured in the same extract sample, and the ratio RNA:DNA was calculated.

PROGRESS: We found that the mean of RNA:DNA ratios was significantly different between normal ovaries and benign ovarian tumors (serous cystadenoma and dermoid cyst). Also, normal ovaries were significantly different from ovarian carcinoma.

274. NUCLEAR DNA STUDY OF GYNECOLOGIC CANCERS

Fu, Y. S., Reagan, J. W., Case Western Reserve University, School of Medicine, Dept. of Pathology, *2109 Adelbert Rd., Cleveland, Ohio,* 44106, United States of America

The proposed work involves quantitation of the nuclear DNA content of the premalignant and malignant neoplasms of the female genital tract using the technique of Feulgen microspectrophotometry. Based on the distribution of the nuclear DNA content, the ploidy pattern (euploidy, polyploidy and aneuploidy), modal values of the stem-cell lines and the cell cycle kinetics are determined. The results of the current work indicate that the biologic potential and the prognosis of the lesion are closely related to the nuclear DNA aberrations.

275. CYCLIC GMP LEVELS IN GYNECOLOGIC NEOPLASMS

Duttagupta, C., Yeshiva University, Bronx Campus, Albert Einstein School of Medicine, Dept. of Gynecology & Obstetrics, *1300 Morris Park Ave., Bronx, New York,* 10461, United States of America

This proposal is designed to determine the usefulness of cyclic GMP, cyclic AMP assays or their calculated ratios in plasma and urine of patients with gynecological malignancies. As a potential measure of cellular proliferative activity, attention will also be focused upon obtaining data as to whether such values may be useful in the screening, detection, diagnosis and treatment of estrogen dependent neoplasms in the human female.

276. COLLECTION OF SERIAL SERUM SAMPLES FROM CANCER PATIENTS

Feit, C., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York,* 10021, United States of America

OBJECTIVES: Collect serial serum samples (minimum 10 ml each) before therapy and at regular intervals thereafter from patients with melanoma, ovarian carcinoma, lung carcinoma, and Hodgkin's disease, plus samples from suitably matched patients with benign skin lesions, benign adnexal masses, a history of heavy smoking, and benign lymphadenopathy to serve as controls. Provide that careful follow-up evaluations of the patients will be made using designated forms, and a minimum of twenty-five persons in each disease category will be followed. Store samples at minus 70 degrees Celsius in 1 ml aliquots for the purpose of periodic shipment to a central serum bank or to investigators designated by the Project Officer.

277. ROLE OF SELECTED COENZYMES IN ENDOMETRIAL FUNCTION (BABOONS)

Boots, L. R., University of Alabama in Birmingham, School of Community & Allied Health, Dept. of Nutrition Sciences, *Tidwell Hall BOO6, University Station, Birmingham, Alabama,* 35294, United States of America

This is part of a broader project. A summary of this subproject is not available.

B. IMMUNOLOGY OF GYNECOLOGICAL CANCERS

278. IMMUNITY TO HUMAN OVARIAN TUMORS AND CHEMOTHERAPY

Haskill, J. S., Becker, S. E., Fowler, W. C., Walton, L. A., University of North Carolina, Chapel Hill Campus, School of Medicine, Dept. of Obstetrics & Gynecology, *Manning Dr., Chapel Hill, North Carolina,* 27514, United States of America

OBJECTIVE: To investigate the relationship between mononuclear cell infiltration of primary ovarian cancer and the subsequent survival of the patient. Although prognosis is reported to be better when a mononuclear infiltrate is present, there has never been an investigation of the nature, function and potential role of these inflammatory cells. The question of whether or not this reaction is immunologic in nature or simply a non-specific reaction to tumor cell death has not been answered. We have developed a methodology which has been exploited to investigate the relationship between systemic and in situ tumor immunity in a wide variety of animal models. It seemed important to extend these studies to the clinic and, in particular, to ovarian cancer. These patients have generally poor survival rates and large tumor burdens, and they routinely produce large quantities of malignant effusions. In spite of this, many patients show remarkable response to chemotherapy and there are wide variations in the proportions of inflammatory cells and tumor cells recoverable from their tumors and effusions.

Our initial investigations have concentrated on isolating the infiltrating cells present in these tumors and characterizing the various fractions by a variety of membrane and cytoplasmic markers. We have initiated a study of the functional capacity of these cells in a series of tests for non-specific immune reactivity - PHA, NK and ADCC. Our future studies will concentrate on the activity these cells have in relation to the autologous tumor cells both in preparations derived from solid tumors and in ascites.

279. MONONUCLEAR PHAGOCYTES IN HUMAN OVARIAN CARCINOMA

Mantovani, A., Spreafico, F., Mangioni, C., Istituto di Ricerche Farmacologiche Mario Negri, Dept. of Tumor Immunology & Chemotherapy, *Via Eritrea 62, 20157 Milan, Italy*

The investigations proposed herein are designed to elucidate basic aspects of the immunobiology of monocytes and macrophages in human ovarian tumors. Mononuclear phagocytes will be isolated from the peripheral blood and ascitic tumors of patients with epithelial ovarian neoplasms and their cytolytic activity will be measured using in vitro tumor cell lines. Cytotoxicity of mononuclear phagocytes will be compared to that of peripheral blood monocytes and peritoneal macrophages of age-matched patients with non malignant diseases. Attempts will also be made to isolate and test macrophages from primary solid ovarian tumors. In parallel experiments, primary ovarian carcinoma cultures from peritoneal effusions and solid tumors will be analyzed for their susceptibility to macrophage cytotoxicity (lysis and/or stasis). We will also investigate whether stimuli, such as endotoxin and lymphokines, effective in experimental murine systems can enhance the cytocidal capacity of mononuclear phagocytes of ovarian carcinoma patients or control subjects. It is expected that the present study will provide experimental evidence relevant to a better understanding of the role of mononuclear phagocytes in the control of human neoplasia.

280. NATURAL TUMOR CELL KILLING IN HUMANS

Koren, H. S., Fischer, D., Jensen, P., Duke University, School of Medicine, Dept. of Microbiology & Immunology, *Box 3711, Durham, North Carolina*, 27710, United States of America

Natural killing (NK) is described as the cytotoxic activity of lymphoid cells occurring in the absence of any apparent stimulation and directed against certain target cells. In the human, the activity seems to reside in a minor mononuclear lymphoid cell population having receptors for the Fc portion of Ig, lacking detectable SIg and phagocytic activity. The specificity of NK is unclear though the killing is selective. The object of the work proposed here is to investigate the exact nature and possibly heterogeneity of the effector cells involved in NK, and their specificity. Characterization of NK cells will be performed with NK cell enriched population obtained by the application of specific cellular and subcellular immunoadsorbent. We will search for cell markers characteristic of NK cells by using sera from sensitized individuals (multiparous women and hypertransfused patients). The possible relationship of NK to antibody dependent cellular cytotoxicity (ADCC) will be explored by using normal cells and cells from X-linked agammaglobulinemia patients that lack ADCC but have NK activity. In light of the possibility that NK has in vivo relevance to tumor resistance we will evaluate the level of NK in material obtained from ovarian cancer patients. NK activity of patients will be compared to that of controls by testing the effector cells against autochthonous and allogeneic tumor targets. Genetic factors associated with NK will be studied using families with known genetic background. The overall aim is to clarify the nature and specificity of the effector cells and their possible role in ovarian cancer.

BIBLIOGRAPHIC REFERENCES: Koren, H.S., Anderson, S.J., and Larrick, J.W.: In vitro activation of a human macrophage-like cell line. Nature 279: 328, 1979. Jensen, P., Amos, D.B., and Koren, H.S.: Depletion of NK by cellular immunoadsorption. J. Immunol. 123: 1127-1132, 1979.

281. CELLULAR AND HUMORAL IMMUNE RESPONSE IN CERVICAL CANCER

Suarez, M., Ojeda, J. M., Cortes, P., Universidad de Chile, Fac. de Medicina, Dept. de Microbiologia y Parasitologia, *Casilla 6539, Santiago, Chile*

OBJECTIVE: To evaluate the cellular and humoral immune response in patients with premalignant and malignant stages of cervical cancer.

METHOD: Cellular immune response in these patients is being investigated by microcytotoxicity assays. The target cells used are AdGo, DiVa and HeLa cells derived from uterine cervix carcinoma and HEp-2 established from a carcinoma of the larynx. The effector cells are lymphocytes obtained from peripheral blood of cancer patients and matched controls. The blocking effect of patient serum on lymphocyte cytotoxicity is also being investigated.

Studies on humoral immune response are focused on the detection of complement-dependent cytotoxicity antibodies against the target cells mentioned above in the sera of patients and of controls.

282. CIRCULATING IMMUNE COMPLEXES IN PATIENTS WITH CANCER - CORRELATION WITH ESTABLISHED TUMOR MARKERS (ABBREV)

Begent, R. H., Chester, K. A., Charing Cross Hospital, Dept. of Medical Oncology, *Fulham Palace Rd., London, W6 8RF, England, United Kingdom*

OBJECTIVE: (1) To correlate levels of circulating immune complexes (CIC) with levels of established tumor markers in patients with cancer. (2) To isolate immune complexes from serum and identify their components.

APPROACH: Levels of CIC will be measured by quantitation of IgG precipitated by 2% polyethylene glycol. These levels will be correlated with serum human chorionic gonadothrophin (HCG) and alpha fetoprotein (AFP) in patients with malignant teratoma with HCG in gestational choriocarcinoma and with an ovarian tumor antigen in carcinoma of the ovary.

Attempts will be made to identify the antigen components of CIC. Serum will be submitted to gel filtration followed by protein A-Sepharose column chromatography to isolate CIC. Components of the CIC may then be identifiable by polyacrylamide slab gel electrophoresis.

283. CIRCULATING IMMUNE COMPLEX LEVELS IN PATIENTS WITH CANCER OF THE REPRODUCTIVE TRACT

Symonds, E. M., Baldwin, R. W., Clarke, A. G., Faratian, B., University of Nottingham, Cancer Research Campaign Lab., Dept. of Obstetrics & Gynecology, *University Park, c/o City Hospital, Nottingham NG7 2RD, England, United Kingdom*

OBJECTIVE: To investigate whether circulating immune complexes (CIC) in patients with various gynecological tumors and pretumorous disorders can be used to monitor tumor growth, detect early cancers, monitor cytotoxic therapy and enable recognition of recurrence.

APPROACH: Since it is clear that there is no single method of assaying for CIC in patients with gynecological tumors, we propose to use new assay systems on the sera of new and previous patients. These include a comparative study of C1q precipitation with and without the addition of heparin, Con A conglutinin assay and polyethylene-glycol precipitin assay.

PROGRESS: The C1q precipitation assay with and without the addition of heparin has shown that CIC in the sera of pre-operative ovarian patients, of patients with cervix dysplasia, and of patients with carcinoma of the vulva and body of the uterus are not elevated.

In the presence of heparin, however, in sera of patients with cervical carcinoma in situ and invasive cervical carcinoma and in post-operative ovarian sera, CIC are elevated. We have evidence to suggest that heparin may enhance the sensitivity of the binding CIC detected in sera without heparin.

284. CYTOLYTIC AND CYTOSTATIC ACTIVITY OF HUMAN MONOCYTES AND MACROPHAGES IN NORMAL SUBJECTS AND OVARIAN CANCER PATIENTS

Mantovani, A., Luini, W., Candiani, G. P., Polentarutti, N., Istituto di Ricerche Farmacologiche Mario Negri, Dept. of Immunology, *Via Eritrea 62, 20157 Milan, Italy*

OBJECTIVE: The present investigation was designed to study the in vitro interaction of human monocytes and macrophages with tumor cells and the biological mechanisms involved in the regulation of the cytotoxic potential of these effector cells.

APPROACH: Mononuclear phagocytes are isolated by adherence from various anatomical sites (blood, peritoneal exudate, milk, benign ovarian cystic fluid, broncho-alveolar lavages, ovarian tumors) and their in vitro interaction with tumor cells is measured by cytolysis and cytostasis assays. Lymphokines are produced by culturing lymphocytes with antigens or mitogens and their effect, together with that of type I partially purified interferon, is measured by the above mentioned assays.

PROGRESS: Results obtained during this period and current views of this group on human macrophage-mediated natural cytotoxicity and on its regulation will be published.

285. LYMPHOCYTE CYTOTOXICITY IN PATIENTS WITH CERVICAL CANCER

Cortes, P., Suarez, M., Ojeda, J. M., Universidad de Chile, Fac. de Medicina, Dept. de Microbiologia y Parasitologia, *Casilla 6539, Santiago, Chile*

OBJECTIVE: Cellular immune response in cervical cancer patients is being investigated by microcytotoxicity assays. The target cells used in these experiments are derived either from uterine cervix carcinomas (AdGo and HeLa cells) or from larynx tumor (HEp-2).

METHOD: Lymphocytes from cervical cancer patients are cytotoxic against AdGo and HeLa cells; this effect is not observed when the same lymphocyte suspension is assayed against HEp-2 cells. Control lymphocytes from healthy donors do not exhibit cytotoxic activity directed against any of the target cells employed.

PROGRESS: These results suggest the presence of tumor-associated antigens on the surface of HeLa and AdGo cells, as well as the occurrence of sensitized lymphocytes, which react with these antigens, in cervical cancer patients' blood.

286. PURIFICATION AND CHARACTERIZATION OF OVARIAN CANCER-ASSOCIATED ANTIGENS

Lloyd, K. O., Sloan Kettering Inst. for Cancer Research, Human Cancer Serology Laboratory, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

287. TUMOR IMMUNOLOGY - PHOSPHATASE ISOENZYMES

Doellgast, G. J., Chen Wei, S., Wake Forest University, Bowman Gray School of Medicine, Dept. of Biochemistry, *300 S. Hawthorne Rd., Winston Salem, North Carolina*, 27103, United States of America

This research project deals with immunochemical studies on human placental alkaline phosphatase variants obtained from placentae and cancer patients. Progress during the past year has included definition of antigenic sites specific for the cancer variant enzyme by using absorbed rabbit antisera and monoclonal antibodies. Objectives for the current year include continuing to analyze these variant enzymes by generating other monoclonal antibodies and initiating studies on the chemical structures of these enzymes.

The occurrence of this enzyme on membrane fragments in cancer patient ascites fluids has been of some interest to us, and studies on this enzyme form are being continued.

Nude mice carrying a variety of gynecological tumors which have placental-type phosphatase are also being studied.

BIBLIOGRAPHIC REFERENCES: Doellgast, G. J.: Preparation of variant-specific anti-human placental phosphatase antiserum by immunoabsorption. Biochem. Biophys. Res. Commun. 86:661-666 (1979). Wei, S.-C., and Doellgast, G. J.: Specificity of allozyme-absorbed antisera to human placental alkaline phosphatase for individual phenotypes. Biochem. Gen., in press (1980).

288. HUMAN CANCER SEROLOGY

Old, L. J., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

The two objectives of the Human Cancer Serology Program are: I. Serological definition and biochemical characterization of distinctive cell surface antigens of human cancer and II. immunovirologic analysis and biochemical characterization of human cancers of suspected viral etiology. The proposed studies relate to two central questions concerning human cancer: Do human tumor-specific antigens exist and do viruses play a role in the etiology of human cancer? The technique of autologous typing of malignant cells will be used to analyze cell surface antigens of malignant melanoma, renal cancer, astrocytoma, leukemia, lymphoma, and ovarian cancer, and will be applied to breast, lung, and colon cancer as improved methods for the in vitro propagation of these cancers are developed. Serological definition of tumor-specific cell surface antigens of human cancer will be followed by: a) Genetic analysis to determine the chromosomal loci specifying these antigens, b) search for natural antibody to these antigens in the normal human population, c) biochemical characterization, d) assessment of the clinical significance of humoral immunity to these antigens in patients with cancer, and e) development of maximally immunogenic forms of cancer vaccines. Immunovirological studies will focus on selected human cancers that are suspected from serological, virological, and epidemiological evidence to be related to herpesviruses or papovaviruses. The following associations will be investigated: The relation of cytomegalovirus to Kaposi's sarcoma, genital cancer, and colon cancer; the relation of Epstein-Barr virus to nasopharyngeal cancer, and the relation of BK and JC papovaviruses to brain cancer, renal cancer, and cancers developing in immunodeficient patients. Using a variety of serological assays and reference viral antigens and antibodies to identify the range of herpesvirus and papovavirus antigens, evidence will be sought for the presence of viral antigens in human cancer cells and for the occurrence of corresponding antibody in patients with cancer as compared with the normal population.

289. IMMUNOLOGIC ASPECTS OF CANCER

Fisher, R. I., Van Haelen, C., Young, R. C., Wunderlich, J. R., Mann, D., Jaffe, E., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Medicine Branch, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The purpose of this project is to study alterations in the immune system caused by malignancy and chemotherapy. Analysis of the non-specific immune system in patients cured of Hodgkin's disease with MOPP chemotherapy reveals that the patients are significantly immunosuppressed for more than 12 years. An ongoing study has demonstrated that patients with active Hodgkin's disease and patients cured of Hodgkin's disease are more sensitive to a macrophage suppressor cell than normals. Further studies are underway to characterize the genetics of this increased sensitivity to suppression. Diffuse histiocytic lymphoma patients treated with similar combination chemotherapy do not have significant immunosuppression. A unique B cell defect in the immune system of patients with ovarian cancer has recently been published. The chemotherapy and immunotherapy sensitivities of an animal model of ovarian cancer have been described. Studies of combined modality therapy are currently underway. Human peripheral blood lymphocytes cytotoxic to autologous ovarian tumor are being developed in vitro. The immunosuppressive properties of chlorozotocin are being analyzed in a phase II clinical study.

BIBLIOGRAPHIC REFERENCES: Atkinson, J.P., Fisher, R.I., Reinhardt, R., and Frank, M.M.: Reduced concentrations of the first component of complement in hypogammaglobulinemia: correction by infusion of gamma globulin. Clinical Immunol. and Immunopath. 9: 350-355, 1978. Mandell, G.L., Fisher, R.I., Bostick, F., and Young, R.C.: Ovarian cancer: a solid tumor with normal cellular immunity but abnormal B cell function. Am. J. Med. 66:621-624, 1979.

290. THE EFFECT OF RADIATION ON HUMAN CELLULAR IMMUNITY

Onsrud, M., Thorsby, E., Universitetet i Oslo, Rikshospitalet, Vevstypelaboratoriet, *Oslo, Norway*

OBJECTIVE: To characterize the in vitro and in vivo radiosensitivity of periferal blood mononuclear cells (PBM) in healthy persons and patients with uterine carcinomas undergoing external pelvic irradiation.

APPROACH: By co-culturing human T-lymphocytes with TNP-treated autologous B-lymphocytes and macrophages for 10 days in vitro, sensitization to TNP-treated autologous cells can be detected in a proliferative assay. By restimulation with TNP-treated and non-treated autologus cells the TNP-specific response is measured after 3 days. This proliferative response to 'altered self' is tested after different modalities of irradiation.

C. HISTOPATHOLOGY AND CYTOLOGY OF GYNECOLOGICAL CANCERS

291. AMEBIASIS AND DYSPLASIAS OF THE UTERINE CERVIX

Narvaez, C. R., Sociedad de Lucha Contra el Cancer, Depto de Citologia, *Casilla 1060, Quito, Ecuador*

Amebiasis of the uterine cervix is not uncommon in Ecuador, although it has not been described in the literature.

The objective of this study is to analyze the clinical, cytologic and histopathologic aspect of cervical amebiasis and its possible relationship to dysplasias of the cervix.

292. UTERINE CERVICAL DYSPLASIA AND ITS RELATION TO CERVICAL CANCER

Seth, P., Mohapatra, L. N., Luthra, U. K., Kochar, M., Kotwani, B. G., Khurana, B. B., All India Inst. of Medical Sciences, Dept. of Microbiology & Virology, *Ansari Nagar, New Delhi 110016, Delhi, India*

Evidence on the etiopathogenesis and biological behavior of cervical dysplasia is mostly controversial, however, it is generally accepted that less than five percent of cases progress to squamous cell carcinoma. A multifaceted approach to the study in two phases is planned, the first collecting data on the clinical, cytopathological and virological status of dysplasia cases and matched control women and the second following up dysplasia cases and controls to understand the biological behavior of the lesions and their progression to cervical cancer. So far serum samples from 186 patients with cervical dysplasia and 98 normal matched control women have been assayed for herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) antibodies by the indirect hemagglutination (IHA) test. The distribution of HSV antibodies did not vary significantly among cases and controls. Ninety-five women with dysplasia and 39 controls were followed up for periods ranging from 6 to 36 months. The clinical and cytopathological findings of patients with cervical dysplasia were correlated with HSV-1 and HSV-2 antibody profiles in serum from the same patient. It was observed that (1) the majority of dysplasias reverted back to normal cytology during this period; (2) 14 patients had persistent dysplasia of the cervix and all of them had HSV antibodies; (3) three patients developed squamous cell carcinoma of the cervix and one developed adenocarcinoma. All the squamous cell carcinoma patients had HSV-2 antibodies, while patients with adenocarcinoma did not have HSV-2 antibodies. The study continues.

293. SUBEPITHELIAL CONNECTIVE TISSUE IN DYSPLASIAS - IN SITU AND INVASIVE CARCINOMA OF THE UTERINE CERVIX

Rieper, J. P., Fonseca, N. M., Ponciano, B. R., Universidade Federal do Rio de Janeiro, Inst. of Gynecology, Dept. of Oncologia, *Rua Moncorvo Filho 90, Caixa Postal 1191, Rio de Janeiro, Guanabara, Brazil*

OBJECTIVE: To study the behavior of subepithelial connective tissue of the uterine cervix, taking into consideration all the elements that comprise the target tissue cells, fibers, fundamental substances such as blood vessels, lymph and nerves. A comparison of normal cases with cases of inflammation, epithelial dysplasias, invasive or in situ carcinoma will be made to determine changes in connective tissue that may be due to epithelial alterations or which may develop in parallel or which permit the invasion of cancerous epithelium. Metabolic and morphologic differences in the various elements of connective tissue will be studied to identify among other modifications, those in the nerve endings which could be the primary cause of cancer, according to prior study by the authors.

METHOD: Study the composition of connective tissue and nerve endings of the uterine cervix by histologic, histochemical and immunofluorescence methods.

MATERIAL: Biopsy and surgical excisions of the ecto- and endocervix in patients with normal, dysplastic and invasive or in situ cervical carcinoma.

294. STUDY OF DEFICIENCIES AND CYTOLOGIC REPERCUSSIONS

Pontes Cunha, M., Programa Nacional de Controle do Cancer Cervico Uterino, *262 Rua das Gracas, CEP 50.000, Recife, Brazil*

OBJECTIVE: To study cytologic alterations associated with deficiency, their behavior and relation to dysplastic lesions.

METHOD: A group of patients who belong to the Maternal/Infant Program and who are at high risk of developing cervico-uterine cancer will be studied. Two professionals from the Centro de Citodiagnostico, as well as from the Maternal/Infant Program and the Nutrition Program, will participate in the study. Findings will be turned over to the Divisiao Nacional de Doencas Cronico-Degenerativas for an epidemiologic study.

295. MORPHOMETRIC MEASUREMENTS IN HUMAN CANCER

Wiernik, G., Bradbury, S., Spriggs, A. I., Cowdell, R. H., Plant, M., University of Oxford, Research Inst., *c/o Churchill Hospital, Oxford, England, United Kingdom*

OBJECTIVES: Quantitative microscopy of carcinoma of the human cervix uteri and normal cervical tissues in order to achieve an earlier correct prediction of the development of an invasive tumor.

APPROACH: Morphometric analysis has been performed of squamous epithelial cells in biopsy specimens obtained either from patients with proven invasive squamous cell carcinoma or from patients with histologically proven normal cervices. This has shown that when this data is submitted to a programme of multivariate analysis a highly significant difference can be demonstrated (Wiernik, Bradbury, Plant, Cowdell and Williams, 1973, Brit. J. Cancer, 28, 488-499). Parameters that have been measured include nuclear area, ribosomes, fibrils, surface density, inter-cellular space, etc. The methodology is currently being adapted for the direct examination of cervical smear specimens.

PROGRESS: In order to obtain data concerning the premalignant phases of cervix uteri disease, cone biopsy specimens from patients with dysplasia and carcinoma-in-situ are being analysed and will be compared with the data from the normal and invasive cancer specimens. Cervical smears taken at the time of diagnosis of patients with normal histological features and of patients in whom a histological diagnosis of invasive squamous cell carcinoma was made are being analysed by a modified methodology to establish a similar quantitative discrimination. Cervical smears from patients now presenting with invasive carcinoma, taken over the previous decade or more, are also being analysed in a similar manner to ascertain the earliest time when reliable predictive data can be derived.

296. CYTOGENETIC AND ULTRASTRUCTURAL STUDIES ON CERVIX CANCER AND HERPES-INFECTED CELLS

Heneen, W. K., Habib, Z., Lunds Universitet, Wallenberglaboratoriet, *S22101 Lund 7, Sweden*

OBJECTIVES: (1) To determine if patients with cancer or dysplasia of the cervix have specific chromosomal features that imply a greater disposition for cancer. (2) To investigate whether there is any correlation between cervix cancer and herpes virus (HSV-2) infection.

APPROACH: Different banding techniques are used for chromosomal analysis of cervix tumor cells as well as blood cells from the same patients. The chromosomes are also studied in blood cells from patients with cervix dysplasia. The cytological findings in these patients will be compared with the chromosome picture in cultured human cells that are infected or transformed by herpes simplex virus type 2. The ultrastructure of tumor and herpes-infected cells will also be studied.

PROGRESS: Preliminary results indicate that heteromorphism in constitutive heterochromatin (especially in chromosome 1) occurs frequently in patients with cancer and dysplasia of the cervix.

297. PROSPECTIVE STUDY OF PATIENTS WITH INTRAEPITHELIAL NEOPLASIA TREATED WITH ABLATIVE DIATHERMOCOAGULATION

Salas, C. O., Paredes, A., Toledo, P., Iglesias, J., Universidad de Chile, Dept. of Patologia Cervical, *1058 Av. Bernardo O'Higgins, Santiago, Chile*

OBJECTIVE: To perform a prospective analysis of the utilization of ablative diathermocoagulation (DTC) in patients with various grades of intraepithelial neoplasia, mild dysplasia, moderate dysplasia, and in exceptional cases, carcinoma in situ.

APPROACH: Follow-up of patients began 90 days after DTC using cytology and colposcopy. In cases of suspected residual lesion, histologic study of the exocervix and/or endocervical curettage are carried out.

PROGRESS: To date it has not been necessary to complete treatment of any case with surgery. (Translated)

298. RESEARCH INTO VARIATIONS IN HUMAN TISSUES RADIOSENSITIVITY ACCORDING TO CIRCADIAN OSCILLATIONS

Cionini, L., Biti, G., Pacini, P., Mungai, V., Ciatto, S., Ponticelli, P., Magrini, S., Becciolini, A., Balzi, M., Universita degli Studi di Firenze, Istituto Interfacolta di Radiologia, *Viale Morgagni, c/o Policlinico Universitario, 50144 Florence, Italy*

Circadian oscillations of the cellular proliferation have been observed in several proliferating tissues and in non-proliferating tissues induced to regenerate. The existence of such oscillations has been confirmed in some tumors of laboratory animals and data also exist on skin tumors of man. As the cellular radiosensitivity is known to be cycle dependent, timing of irradiation can be supposed to modify the cellular response to irradiation. Research carried out at the Radiobiology Laboratory of this Institute demonstrates that the intestinal damage in rats varies to a considerable degree depending on the timing of irradiation. Based on this assumption, this project has been devised with the two follow-up goals: 1) to evaluate the existence of different degrees of the radioresponse depending on the time of irradiation in human tissues as well, and 2) to evaluate the possibility of using this phenomenon to increase the therapeutic ratio in radiotherapy of tumors.

The clinical part of the project has now begun. Patients selected for the project are mainly those affected by cervical cancer, which is easily observable and available for multiple biopsies.

The project includes the clinical observation of the skin and mucosal reaction and of the neoplastic regression, the determination of some biochemical indicators of the radiation injury, and the in vitro incorporation of 3H-tymidine.

Patients have been divided into two groups according to the time of irradiation: Following the experimental observations on the rats, the irradiation has been performed between 7 and 9 a.m. in the first group and between 6 and 8 p.m. in the second group.

299. CYTOHISTOPATHOLOGIC CORRELATION OF CERVICAL LESIONS

Bernal, B. S., Villagran, L. J., Secretaria de Salubridad y Asistencia, Direccion de Lucha contra el Cancer, *Manuel Acuna 2736, Guadalajara 6, Jalisco, Mexico*

OBJECTIVE: To correlate the results of vaginal cytology, biopsy, and histologic study of cervical cones and hysterectomies.

METHOD: The patients under study are patients with abnormal cytology sent to the hospital for treatment.

PROGRESS: To date, 20 cases have been studied.

300. MECHANISMS AND MANIFESTATIONS OF CARCINOMATOUS CHANGE IN HUMAN AND EXPERIMENTAL CANCER

Fox, C., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Laboratory of Biochemistry, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The research reported covers a multidisciplinary program for the early diagnosis of human cancer and for studying metastatic properties of cellular attachment. The attachment of epithelial cells and of fibroblasts to surfaces was studied by a newly modified reflexion contrast microscope. The malignant potential of cervical condylomata accuminata was assessed in a patient population of 190,000 well women. A third study concerns the identification of primary human breast cancers with their metastases using quantitative measurements of individual cellular DNA distribution. A fourth study has been involved in establishing new morphometric and cytochemical markers for highly differentiated urothelial cancers. The potential of fine needle aspiration biopsy for obtaining new parameters for estimating prognosis and further diagnosis of primary and secondary human cancers was explored. A continuing study of carcinogen metabolism included effects of anti-oxidants on metabolism of polycyclic aromatic hydrocarbons. A study of the kinetics of cellular growth in cervical epithelium was conducted to determine the viability of cervical epithelium after exposure to carcinogens.

BIBLIOGRAPHIC REFERENCES: Auer, G., Arrhenius, E., Granberg, P.-O, and Fox, C.H.: Comparison of DNA distributions in primary human breast cancers and in their metastases. Eur. J. Cancer 16: 273-278, 1980. Bereiter, J., Fox, C.H., and Thorell, B.: Quantitative reflection contrast microscopy of living cells. J. Cell Biol. 82: 767-779, 1979.

301. GYNECOLOGICAL CYTOLOGY REGISTRY, NOVA SCOTIA

Anderson, G., Robinson, S. C., Fraser, R. C., Victoria General Hospital, *5788 University Ave., Halifax, Nova Scotia*, B3H 2Y9, Canada

The summary for this project is under entry no. 197.

302. PROFESSIONAL EDUCATION IN CYTOLOGY RELATED TO CANCER

Blair, O., St. Louis University, School of Medicine, *1402 S. Grand Blvd., St. Louis, Missouri*, 63104, United States of America

The summary for this project is under entry no. 204.

303. PROFESSIONAL EDUCATION IN CYTOLOGY

Barker, E. A., University of Washington, School of Medicine, Dept. of Pathology, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

The summary for this project is under entry no. 205.

304. ENDOMETRIAL ADENOCARCINOMA-ASSOCIATED OVARIAN PATHOLOGY

Reeves, G., Navarini, H., Arcangeli, O., Fragapane, S., Marun, M., Valenti, J. L., Malamud, L., Avedision, J., Bicocca, C., Celoria, G., Cerro, E., Colabianchi, J. C., Universidad Nacional de Rosario, Facultad de Ciencias Medicas, Catedra de Patologia, *Santa Fe 3100, 2000 Rosario, Argentina*

OBJECTIVES: To determine the frequency of morphologic abnormalities of the ovary in patients with endometrial adenocarcinoma (EAC). To study the nature of the ovarian pathology (OP) found. To correlate these findings with other clinical and pathologic variables in order to detect the importance of OP in the induction, diagnosis, treatment and outcome of EAC. To determine, if possible, better ways of early diagnosis and treatment of patients with OP causally related to the appearance of EAC.

METHODS: The material will be obtained from private and welfare hospitals of the city of Rosario with a stable population of 1 million people and through gynecologists and pathologists affiliated to GEO. The clinical records, the pathology reports and the available pathology slides, paraffin blocks and/or wet tissue stock from patients that have undergone adnexohysterectomy as part of the treatment for EAC, will be critically reviewed and reclassified when indicated. Control cases will be provided when possible for the same age range, socioeconomic status and institution of origin.

PROGRESS REPORT: A test study has already been conducted involving 308 study and 387 control cases. No efforts were made to obtain additional information and the clinical and pathologic diagnoses made in different institutions, by different physicians and within a period from 5 to 20 years were accepted without review. The incidence of OP in EAC cases was double that of controls and was twice as frequent in people under 41 and above 69 years of age. Sterility was high in the EAC group and its frequency was double that found in EAC cases under 41 years. Non-sterile patients under 41 years had a lower number of pregnancies and offspring and low fertility patients - sterile or with only one pregnancy - contributed the gross of the young population with EAC and were more frequently obese. The presence of OP, in general, tended to produce an early diagnosis of EAC and an early stage of neoplastic development. These findings suggest that OP frequently precedes the development of EAC and is probably operative in its induction. The chief ovarian abnormality is a primary or secondary hyperplasia of the ovarian stroma and, to a lesser extent, the existence of a chronic status of impaired ovulation or functioning tumor.

305. BRENNER TUMOR OF THE HUMAN OVARY

Reeves, G., Sierra, D., Universidad Nacional de Rosario, Facultad de Ciencias Medicas, Catedra de Patologia, *Santa Fe 3100, 2000 Rosario, Argentina*

This project has been initiated to gain a better understanding of the histogenesis of the Brenner tumor. There is agreement among the majority of authors that the surface of 'germinal' epithelium is a most favored source for the Brenner tumor. However, there is still a question regarding the nature of the transformation that this original epithelium undergoes to become Brennerian. A point of greater interest is the understanding of the intimate mixture of the epithelial component of the tumor with the stromal component, which is responsible for the tumor mass in practically all cases. The stromal component is regarded as reactive by the few authors who have superficially dealt with the subject. No explanation has been offered as to how this Brennerian epithelium induces the stromal proliferation or the steps by which the original germinal epithelium gives rise to a commonly solid intraovarian tumor.

The material to be used in this project is available from two major university hospitals, from the private practice of the investigator and from a local registry of ovarian tumors. This registry was initiated in 1973 and most hospitals, pathologists and gynecologists of this city of 1 million inhabitants and of neighboring cities contribute their ovarian pathology. An estimated 80 Brenner tumors with relevant clinical data, and available paraffin blocks, tissue sections or wet tissue stock are registered. There are also 10 more cases which have been collected by the senior investigator over the years and saved in paraffin blocks. These cases have in common their small size, which allows their study by true serial sections. Some have already been studied and special reconstructions have been produced. The principal investigator has been working for years in ovarian pathology, with special attention to the ovarian stroma. This experience is now to be applied to study the stromal component of the Brenner tumor. The mechanisms of participation of the ovarian stroma in the building up of other ovarian tumors (for example, the granulosa cell tumor), a subject which is often neglected and generally poorly understood, is expected to be elucidated. Study of ultrastructural features of the eipithelial component is mandatory to determine several aspects of the whole project. Facilities are available, but the project's funding needs are the major adverse factor causing slow progress and delays. (Text Abridged.)

306. CELL PROLIFERATION IN SOLID HUMAN TUMORS

Rabes, H. M., Carl, P., Rattenhuber, U., Ludwig Maximilians Universitat Munchen, Inst. of Pathology, *Thalkirchner Str. 36, D8000 Munich 2, Bayern, Federal Republic of Germany*

To obtain information on human solid tumor cell kinetics and growth fraction, tumors are perfused immediately after surgical removal in a normothermic perfusion system with an oxygenated medium containing radioactively labeled DNA precursors. Whole tumor autoradiography reveals topography and in combination with enzyme-histochemistry, cytologic specificity of proliferating and non-proliferating tumor cells. Influence of preoperative irradiation is studied with this system. The investigation started using kidney tumors and is now extended to human testicular and ovarian tumors.

307. DIAGNOSTIC HISTOCHEMICAL AND ELECTRON MICROSCOPIC FEATURES OF HUMAN OVARIAN TUMORS

Klemi, P. J., Turun Yliopisto, Dept. of Pathology, *Kiinamyllynk 8-10, SF20500 Turku 52, Finland*

OBJECTIVE: Improvement in diagnosis of ovarian tumors. In order to improve the diagnosing of ovarian tumors various histochemical and electron-microscopic methods will be used.

308. CECAR - A CYTOHISTOLOGICAL METHOD (ABBREV)

Bocanera, R. A., Schlaen, I., Roncoroni, E., Canaves, L., Villa, H., Freyre Hospital, *Olive 1151, Mendoza 1670, 2000 Rosario, Argentina*

The CECAR (for 'cepillo,' brush; 'endometrial,' endometrial; 'cabezal,' bolster; 'articulado,' articulated; 'rotatorio,' rotating) method was applied to 427 women whose ages ranged from 20 to 91, with the average age being 48.2 years. The material thus obtained allowed cytological and histological evaluation by means of conventional cytohistological procedures. Useful material was obtained for diagnosis in 98.4% of the cases. In 89 patients out of the total number of women examined D and C was performed after the CECAR application. False negatives were not found. In five patients, after the cytological evaluation obtained with CECAR, adenocarcinoma of the endometrium was suspected. However, it was not confirmed by histological evaluation obtained with the same CECAR, nor by the D and C, both showing the presence of endometrial polyps.

RESULTS: Twenty-eight benign hyperplasias (simple hyperplasia and cystic glandular hyperplasia), 11 early endometrial lesions, (adenomatous hyperplasia, atypical hyperplasia and adenocarcinoma in situ), and 13 infiltrative endometrial adenocarcinomas were found. The average age for women with carcinomas was 64.8 years, and for women with early endometrial lesions - 49.5 years. Out of 24 patients with early endometrial lesions and carcinomas, 4 did not demonstrate any symptoms at all.

309. EPITHELIAL/MESENCHYMAL INTERACTIONS OF NORMAL AND NEOPLASTIC ADULT HUMAN ENDOMETRIUM IN VITRO

Kirk, D. J., Clingan, D. A., Taylor, R. W., Fairweather, D. V., Imperial Cancer Research Fund, Hormone Biochemistry Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

The studies outlined previously (ICRF Scientific Report 1979 -report 42) are being continued to try to elucidate the mechanism of epithelial repression of stromal growth in vitro. In addition, the effects of stromal cells and/or a collagen growth substratum on epithelial steroid hormone responsiveness are being studied.

310. ENDOMETRIAL CARCINOMA - A STUDY BASED ON WHOLE ORGAN SECTIONS

Grontoft, O., Risberg, B., University of Linkoping, Dept. of Pathology, *S58183 Linkoping, Sweden*

A histopathological comparison will be made between the preoperative curettage and the findings in the operative specimen using whole organ sections in cases of atypical adenomatous hyperplasia and differentiated endometrial carcinoma.

311. CARCINOMA OF THE ENDOMETRIUM

Norris, H. J., U.S. Dept. of Defense, Armed Forces Inst. of Pathology, *c/o Walter Reed Medical Ctr., Washington, District of Columbia,* 20306, United States of America

The diagnosis and management of endometrial hyperplasia, including atypical hyperplasia, for the past 50 years has been one of the most controversial subjects in gynecologic pathology and gynecology. Criteria are poorly defined and confusion exists due to the use of the same terms by pathologists for markedly different lesions. The natural history of endometrial hyperplasia has still not been delineated. These aspects should be classified by our study.

Five hundred cases of endometrial hyperplasia have been obtained from the AFIP files over a 30-year period ending in 1970. These cases are all military, the diagnosis having been made on endometrial curettings only. We would like to determine the fate of these patients after their curettage. Does the hyperplasia regress or does it progress to more advanced hyperplasia or carcinoma? We would like to review the slides if any additional surgical procedures such as a repeat curettage or hysterectomy was performed. It is only through such a 'prospective' analysis that the natural history of endometrial hyperplasia can be determined and the criteria for what constitutes the precursors of endometrial carcinoma defined.

The cases in the AFIP files have been reviewed and the 500 examples of endometrial carcinoma are in the process of being forwarded to the follow-up unit.

312. SARCOMAS OF THE UTERUS

Norris, H. J., Tavassoli, T., U.S. Dept. of Defense, Armed Forces Inst. of Pathology, *c/o Walter Reed Medical Ctr., Washington, District of Columbia,* 20306, United States of America

Follow-up data on 70 endometrial stromal nodules are being tabulated in an effort to answer the question of whether circumscribed margins are benign and infiltrating margins are malignant.

Follow-up data on 30 adenosarcomas are being tabulated in an effort to find out what their clinical and pathological characteristics are and what the criteria for diagnosis should be.

313. SQUAMOUS DIFFERENTIATION IN ENDOMETRIAL CARCINOMA (HUMAN, HAMSTERS)

Silverberg, S. G., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Pathology, *4200 E. 9th Ave., Denver, Colorado,* 80262, United States of America

This is part of a broader project. A summary of this subproject is not available.

314. NEOPLASMS OF VULVA AND VAGINA

Norris, H. J., U.S. Dept. of Defense, Armed Forces Inst. of Pathology, *c/o Walter Reed Medical Ctr., Washington, District of Columbia,* 20306, United States of America

Two manuscripts have been published in 1979 on smooth muscle tumors of the vulva and vagina. They define criteria for leiomyosarcoma for the first time, since we have enough cases to be able to determine what the criteria should be in the vulva and vagina. These criteria will help pathologists decide what is benign and malignant in this area. A review article was submitted on the effect of DES on the vagina. We plan to review some other soft tissue neoplasms and possibly study carcinomas arising in adenosis.

BIBLIOGRAPHIC REFERENCES: Tavassoli, F.A., and Norris, H.J.: Smooth Muscle Tumors of the Vulva. Obstet. Gynecol. 53: 213-218, 1979. Tavassoli, F.A., and Norris, H.J.: Smooth Muscle Tumors of the Vagina. Obstet. Gynecol. 53: 689-693, 1979.

315. CHROMOSOMAL CHANGES IN AMNION AND CHORION CELLS (HUMAN)

Fogh, J. E., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

316. CYTOKINETICS AND CHEMOTHERAPY OF HUMAN SOLID TUMORS

Zubrod, C. G., University of Miami, School of Medicine, Dept. of Oncology, *1400 N.W. 10th Ave., Box 520875, Coral Gables, Florida*, 33152, United States of America

This is an investigational program project aimed at a better understanding of important biological, biochemical and pharmacological factors influencing the growth of selected human solid tumors and their management by chemotherapy.

The research program will focus on the cytokinetics of human solid tumors of the female genital tract, skin (melanoma), head and neck, and lung. Cytokinetics will be analyzed in relation to designing chemotherapy programs with cell cycle specific and cell cycle non-specific drugs for clinical use in patients. Animal studies with athymic nude mice heterogeneously transplanted with these human tumors will be investigated in parallel for cytokinetics and chemotherapy models. Specific studies will be performed regarding the pharmacologic effects of cytotoxic drugs on cytokinetics and drug-directed biochemical pathways in these human tumors in vivo and in vitro. Cell sorting and flow microfluorometry techniques will be used in parallel with classical radioautography in the study of kinetics of patient tumors both in the patient and in the athymic mouse. Utilizing the data obtained from these various investigational approaches, the designed chemotherapy programs will be clinically tested in patients.

317. VAGINAL AND CERVICAL EPITHELIAL CELL CULTURE MODEL

Rice, R. H., Bryant, J. L., Harvard University, Boston Campus, School of Public Health, Dept. of Physiology, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

Based on recent success in cultivation of human epidermal keratinocytes with lethally irradiated mouse 3T3 feeder layers, this project is designed to develop a model system for the study of primate vaginal and cervical epithelial cells in serial culture: 1. Vaginal and ectocervical epithelial cells from normal biopsy tissue will be examined in culture for growth and biochemical properties. First, culture conditions will be optimized for growth rate and differentiated character by variation of epidermal growth factor, cholera toxin, and hydrocortisone concentrations. The density and cell type (3T3 or stromal) of the feeder layer will also be varied. Second, the biochemical markers of the cells (keratins, cross-linked envelopes, glycogen) will be examined to determine the resemblance of the cells to their counterparts in vivo and to epidermal cells. Third, the response of these cells to sex steroid hormones will be studied. The presence of estrogen and progesterone receptors will be examined. 2. The cells from lesions of cervical dysplasia and carcinoma will be cultivated and compared in properties to normal cells by the criteria of growth and differentiated character. The objective is to isolate abnormal cells in culture that are at intermediate stages of transformation. A possible correlation of deficient cross-linked envelope formation with degree of abnormality will be explored. Epithelial cells from biopsy of endocervix will be examined as a necessary control for identification of abnormal cells and for extension of the culture system to pathological conditions such as diethylstilbestrol-induced vaginal adenosis. A long-range goal of this research is to find a source of partly transformed human epithelial cells for use as sensitive targets in testing of chemical carcinogens.

318. CELL CULTURE MODEL FOR CERVICAL AND VAGINAL EPITHELIA AND CERVICAL CARCINOMA

Rice, R. H., Harvard University, Boston Campus, School of Public Health, Dept. of Physiology, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

Based on recent success in cultivation of human epidermal keratinocytes, this project is designed to develop a model system for the study of primate vaginal and cervical epithelial cells in serial culture.

1. Vaginal and ectocervical epithelial cells from normal tissue will be examined in culture for growth and biochemical properties. First, culture conditions will be optimized for growth rate and differentiated character by variations of epidermal growth factor, cholera toxin, and hydrocortisone concentrations. The density and cell type (3T3 or stromal) of the feeder layer will also be varied. Second, the biochemical markers of the cells (keratins, cross-linked envelopes, glycogen) will be examined to determine the resemblance of the cells to their counterparts in vivo and to epidermal cells. Third, the response of these cells to sex steroid hormones will be studied. The presence of estrogen and progesterone receptors will be determined.

2. The cells from lesions of cervical dysplasia and carcinoma will be cultivated and their properties compared to those of normal cells according to the criteria of growth and differentiated character. The objective is to isolate those abnormal cells in culture that are at intermediate stages of transition to malignancy. Epithelial cells from endocervix will be examined as a necessary control for identification of abnormal cells and for extension of the culture system to pathological conditions such as diethylstilbestrol-induced vaginal adenosis.

319. OVARIAN TUMORS IN YOUNG MICE

Beamer, W. G., Jackson Lab., *Box 258, Bar Harbor, Maine*, 04609, United States of America

Granulosa cell tumors of the ovary have been identified in young SWR/J mice. Careful selection of a subline (designated SWR/Wt) has enhanced the incidence to 10 percent. Efforts to demonstrate viruses associated with these tumors have been unsuccessful. Studies are proposed to characterize the morphology and endocrinology of spontaneous and derived tumors; to further increase the incidence of the tumors; to continue preparation of recombinant inbred stocks for genetic analyses; and to begin examination of methods for treatment and prevention of recurrences of granulosa cell tumors.

320. OVARIAN AGING - MORPHOGENESIS OF A SEROUS CYSTADENOMA

Quattropani, S. L., Virginia Commonwealth University, School of Basic Sciences & Graduate Studies, Dept. of Anatomy, *901 W. Franklin St., Richmond, Virginia*, 23284, United States of America

Results of preliminary studies on the guinea pig ovary indicate the presence of ovarian cysts which arise spontaneously and with a high degree of frequency. Morphologically these cysts are similar to the benign serous cystadenoma of human ovaries. The purpose of this proposed study is to define morphologically such cysts and stages of their development as they arise in the ovaries of Hartley strain guinea pigs. Ovaries from animals of various ages will be examined by light and electron microscopy, by histochemistry, and by autoradiography. Information will be sought on changes in tissue and cell structure and permeability, in membrane structure and staining characteristics, and in enzymatic activity related to secretion and transport. The methodologies involved will include scanning and transmission electron microscopy, thymidine incorporation, horseradish peroxidase and lanthanum tracing, lectin staining and electron microscopic demonstration of phosphatase activities. The information derived will be used in future investigations of the cause and control of, and potential for, malignant transformation of this cyst.

VI. SCREENING, DIAGNOSIS, AND PROGNOSIS OF GYNECOLOGICAL CANCERS

A. CERVICAL AND OTHER GYNECOLOGICAL SCREENING PROGRAMS

321. EVALUATION OF CERVICAL CANCER SCREENING

Shigematsu, T., Tada, M., Kitao, M., Nose, T., Saito, K., Fukuoka University, School of Medicine, Dept. of Public Health, *34 Nanakuma Nishi-ku, Fukuoka City 814, Japan*

In Japan cervical cancer screening has been carried out extensively, but no adequate evaluation of its impact has been made. This study aims to evaluate the effect of screening, and to establish the duration of carcinoma in situ and the optimal screening interval by introducing an intensive program in the Dogo district, the biggest of the Oki Islands, with a female population of 10,000, using the Dozen district in the same islands, with a population half that of the study area, as a control. The population at risk has been registered and its movements are checked and the register updated yearly. Screening is done by gynecologists and with a mobile unit using colposcopy. It is hoped to screen more than 90% of the population at risk in five years and to follow them for 10 years. Screening data are arranged according to the register, copies of death certificates are collected and a survey of cervical cancer patients done both in the area and at the hospitals in the surrounding area. The screening data and incidence, prevalence, mortality and end results in diagnosed cancer patients will be analyzed. A similar program is being carried out in another town in the mountain area of the same prefecture. The total female population included in the two programs is about 15,000.

322. POPULATION SCREENING FOR CERVICAL CANCER

Vooijs, P. G., Bekker, B. V., Veling, S., Katholieke Universiteit Nijmegen, Lab. of Cytopathology, Dept. of Pathology, *Geert Grooteplein Zuid 24, Nijmegen, Netherlands*

Cytological screening of the uterine cervix has proved to be a reliable method for detection of early cervical cancer. The degree of acceptance and effectiveness of such a screening program in the Dutch female population is still unknown. To investigate this question, 3 test regions have been created in the Netherlands. One of these is the region around the city of Nijmegen, where women in the age group of 35-54 years are screened every 3 years. The first screening, examining a total of 72,500 women, was done between 1976 and 1979. A second 3-year period will start in August 1979. The accuracy of cytodiagnosis, acceptance of the screening test by the female population, reasons for non-participation and efficacy of organizational procedures are examined. In a long-term follow-up the effects on morbidity and mortality will be calculated. In the whole area (300,000 inhabitants) cervical cancer morbidity is registered.

323. SCREENING FOR CERVICAL CANCER - PREDICTING THE EFFECTS OF VARIOUS SCREENING POLICIES

Habbema, J. D., De Jong, G. A., Van der Maas, P. J., Van Oortmarssen, G. J., Erasmus University of Rotterdam, Dept. of Public Health & Social Medicine, *Wytemaweg 2A, P.O. Box 1738, 3000DR Rotterdam, Netherlands*

A computer program has been developed to simulate the effects of a mass screening policy. This program is applied to the Dutch cervical cancer mass screening program. Special attention is paid to hysterectomies for reasons other than cervical cancer and to the large number of cervical smears that are made outside the mass screening program. Parameters describing the mortality, morbidity, natural history, screening attendance and validity of the test will be collected, either from the literature or by special studies, e.g. the number and age-distribution of smears made outside mass screening programs in Rotterdam 1976-1977, and the incidence and survival rates of cervical cancer patients. These parameters will subsequently be tested in the program in order to reproduce the cervical cancer mortality before mass screening started, and to reproduce the first findings of the current mass screening. Then, alternative screening policies will be simulated in order to compare their expected effects.

324. THE EFFICIENCY OF CERVICAL CANCER SCREENING IN WEST YORKSHIRE

Parkin, D. M., Joslin, C. A., Leeds Area Health Authority, *Claypit Ln., Hepworth House, Leeds LS2 8AP, England, United Kingdom*

The project covers areas of West Yorkshire with varying levels of the incidence of cervical cancer and aims to collect data on a 1:10 sample of all cervical smear examinations performed, with follow-up on all abnormal tests. Incidence data for clinically manifest carcinomas will be obtained from the Cancer Registry. Information on levels of screening, together with the results in the population studied, will be available for comparison with data collected elsewhere. It is intended to mount intervention studies to influence the degree and location of screening, with simultaneous monitoring of the results obtained.

325. THE VALUE AND EFFICIENCY OF CYTOLOGY IN THE CONTROL OF CARCINOMA OF THE CERVIX

Yule, R., Christie Hospital & Holt Radium Inst., Laboratory of Diagnostic Cytology, *Wilmslow Rd., Withington, Manchester M20 9BX, England, United Kingdom*

The aim is to screen as high a percentage as possible of the 1.5 million women at risk in northwest England. To date, over 850,000 women have been examined at least once, and the project continues to determine the age of onset, frequency and interval at which cyto-testing would be best undertaken. Routine recall for screening is based on a computerized record and recall system.

326. CARDIFF CERVICAL CYTOLOGY STUDY

Landsman, J. B., Evans, D. M., Jones, J. M., Sweetnam, P. M., Medical Research Council, Epidemiology Unit, *4 Richmond Rd., Cardiff CF2 3AS, Wales, United Kingdom*

The main objective of the Cardiff Cervical Cytology Study is to evaluate screening for cervical cancer. The study is based on a defined population: all women who have ever been married, aged 25-69, resident within the Cardiff City area. The basic design objective was that all eligible women should be screened three times. The defined population was enumerated by house-to-house visiting, and eligible women were offered appointments for a cervical smear test at specially organized clinics. The study began in late 1965 and the first round of visiting the city finished early in 1971. The defined population numbers some 71,000 women of whom 46,000 (65%) accepted the offer of the test. Subsequent to the first smear women were re-called for second and third smears at two to three yearly intervals. Some 38,000 have so far had a second smear and over 30,000 have had a third. The study should provide estimates of the prevalence and incidence of the various pathological states, and estimates of false negative and false positive error rates. Death and registration rates for invasive cancer in the Cardiff City area are being monitored.

327. EVALUATION OF EARLY DETECTION OF CANCER OF THE CERVIX UTERI BY CYTOLOGICAL SCREENING

Neuser, D., Staedtisches Krankenhaus im Friedrichshain, Zytodiagnostisches Zentrallaboratorium, *Leninalle 49, 1017 Berlin, German Democratic Republic*

Between 1955 and 1969 the situation with respect to cervix carcinoma in Berlin hardly changed; morbidity, mortality, stage distribution and 5-year survival rates remained much the same. It is proposed to test whether cytological screening can lower morbidity and mortality. For this purpose, all women aged 20 to 65 living in Berlin will be cytologically examined every two years. Using the National Central Cancer Registry, the relationship of carcinoma in situ to invasive carcinoma and the stage distribution of the invasive cervix carcinomas and morbidity and mortality before, during, and after screening will be investigated. The first four years were characterized by a considerable increase in carcinomas in situ and a shifting of stages in favor of stages Ia and Ib, with coverage of 80% of the target population. In 1978 a significant decrease in carcinoma in situ (38%) and in invasive cervical cancer (30%) was observed for the first time in the whole female population.

328. EVALUATION OF THE EFFECT OF SCREENING FOR CANCER OF THE UTERINE CERVIX, AND AN ANALYSIS OF NATURAL HISTORY OF THE DISEASE

Johannesson, G., Day, N. E., Geirsson, G. B., Tulinius, H., Krabbameinsfelag Islands, Detection Center, *Sudurgata 22, P.O. Box 523, 121 Reykjavik, Iceland*

A nationwide program of early detection of cervical cancer has been in operation since 1964, with over 80 percent coverage of women under 70 years of age. A drop in mortality from the disease, clearly associated with the screening operation, has been observed since 1970 (International Journal of Cancer 21, 418-425, 1978). The present study is investigating the rate of progression from normal to atypical to malignant cytology, to establish the most effective and economic screening patterns.

329. RETROSPECTIVE EVALUATION OF THE PAPANICOLAOU SMEAR IN THE PREVENTION OF INVASIVE CERVICAL CANCER

Clarke, E. A., Anderson, T. W., University of Toronto, Faculty of Medicine, Dept. of Preventive Medicine & Biostatistics, *92 College St., Toronto, Ontario*, M5S 1A8, Canada

OBJECTIVE: The objective of this study is to test the hypothesis, using a case-control study, that part of the decrease in the incidence of invasive carcinoma of the cervix is due to screening by the Papanicolaou ('Pap') technique.

APPROACH: Eligible cases were all patients with newly diagnosed carcinoma of the cervix admitted to a large cancer hospital during a three year period. 212 cases and 1060 neighborhood controls were interviewed to obtain information about risk factors and all 'Pap' smears taken in the previous ten years. Subsequently, confirmation of the 'Pap' smear history was obtained from attending physicians. Significantly fewer of the cases (27%) than the controls (52%) had had at least one 'Pap' smear in the absence of symptoms in the five years prior to diagnosis of the index case (p less than 0.0001). Expressed as a risk ratio, these figures indicate that asymptomatic women who have not had any 'Pap' tests in the previous 5 years are at 3.3 times the risk of developing symptomatic cervical cancer. Controlling for known risk factors such as socio-economic status, age at first intercourse, etc., the risk remains constant.

330. PROGRAM OF PREVENTIVE TOCOGYNECOLOGY AS PART OF A GENERAL MEDICAL SERVICE

Pinotti, J. A., Brenelli, H. B., Moragues, J. D., Pastene, L. L., Barini, R., Bigatti, L. E., Universidade Estadual de Campinas, Faculdade de Ciencias Medicas, *Rua Benjamin Constant 1657, Caixa Postal 1170, Campinas 13100, Brazil*

OBJECTIVE: Based upon the results of the preventive tocogynecology program, it was determined that a gynecological checkup should be included as a part of the medical care of the general adult out-patient service. The purpose is to detect asymptomatic gynecologic pathologies, treat them, and educate the women regarding the importance of preventive gynecology.

METHOD: A multidisciplinary team will instruct all women who come to the service and will perform the exam, including tocogynecology, speculum, cytology and breast exam.

PROGRESS: During the first six months 2,346 patients were examined, 45% of whom presented with some form of gynecologic pathology. Another 35.5% were referred to the out-patient breast service, where 61 were found to have benign pathology and 6 presented with breast cancer. Benign gynecologic pathology was evident in 148 patients (dystopia and uterine myoma); of 13 altered cytologic examinations, 4 corresponded to cancer of the uterine cervix. This program is proving to be of great usefulness, low cost, and is feasible without sophisticated equipment. It is considered a valuable addition to all services attending a female population.(Translated)

331. SIMPLIFIED GYNECOLOGIC EXAMINATION PERFORMED BY TRAINED PARAMEDICAL PERSONNEL

Diaz Moragues, J., Pinotti, J. A., Universidade Estadual de Campinas, Faculdade de Ciencias Medicas, *Rua Benjamin Constant 1657, Caixa Postal 1170, Campinas 13100, Brazil*

In order to take better advantage of the few resources of the General Gynecological Out-patient Service and to attend to female patients, a simplified system of gynecologic exams was initiated in August 1979, manned by specially trained paramedical personnel and medical students under the supervision of a physician.

During the initial three months, 278 patients were examined. Of these, 40.2% were considered normal; 34% were instructed to return for an annual exam; 12% underwent simple pathological treatment; 50.7% were referred for further gynecological examination.

This simple examination has proven sufficient for examining half the patients and for determining by certain examinations the relative frequency necessary in follow-up visits.

The implementation of such a service whereever a female population is examined is recommended. (Translated)

332. PROGRAM OF PREVENTIVE TOCOGYNECOLOGY - PILOT DESIGN FOR INTEGRAL MEDICAL CARE

Diaz Moragues, J., Pinotti, J. A., Universidade Estadual de Campinas, Faculdade de Ciencias Medicas, *Rua Benjamin Constant 1657, Caixa Postal 1170, Campinas 13100, Brazil*

OBJECTIVE: Three years ago a program was initiated for performing a gynecologic checkup of all women visiting the Hospital das Clinicas of the Universidade Estadual de Campinas for any reason whatsoever. The objective of the program is to detect asymptomatic gynecologic pathology and study the viability of a method of choice that would, to a certain point, have a place in a network of primary health care delivery.

METHOD: Using a very simple methodology, 7,320 women were examined by medical students and obstetrical nurses under a physician's supervision. Some form of gynecologic pathology or a condition of high risk was detected in 22.41% of the patients: 0.31% had breast cancer; 0.72% had positive cytologic exams; 11.7% had uterine myoma; and 4.04% had severe genital dystopia.

The routine gynecological checkup has been shown to be useful and important for all women visiting the hospital for any reason; the organizational and economical requirements of this type of service are justifiable.

A similar automatic checkup of male patients is recommended, in order to detect diseases of greatest prevalence. (Translated)

333. A PILOT DEMONSTRATION DETECTION PROGRAM

Greco, V. F., Schulman, N., Tucker, R. S., Teitelbaum, C., Community Cancer Corp. of Luzerne County, *Box 1345, Wilkes-Barre, Pennsylvania*, 18703, United States of America

This pilot detection program is the first effort in implementing a cancer control plan, begun by area physicians several years ago and supported in part by a Cancer Center Planning Grant. The pilot proposes to use specially trained nurse clinicians to perform screening tests and examinations in Luzerne County, Pennsylvania. During the three-year program, nurses, recruited from the community and trained at Hahnemann Oncologic Institute, will perform complete screening examinations in two hospital-based clinics. A projected population of 10,944 people over the age of 40 will be screened for cancer of the mouth, throat, cervix, prostrate, breast, skin, and rectum.

Demonstration pilot efforts include the training and utilization of nurse clinicians in this unique fashion, study of variables in patient participation, acceptance of nurse clinicians by both patients and physicians, examination of the validity and reliability of this form of community based cancer screening, analysis of cost variables and the progressive development of programmatic self-support by the community. The pilot is further designed to encourage the introduction of a single county tumor registry and to encourage additional epidemiologic research in future years although funds are not requested for these purposes here.

The applicant is the Community Cancer Corporation of Luzerne County (CCC), a new non-profit corporation which has been created to plan and manage this and other cancer related service projects. The corporation and indeed this pilot request are an outgrowth of the extremely high incidence of cancer in the county, the high degree of physician and community support for the project and the potential applicability of the pilot to other similar regions of the country.

334. OPTIMIZATION OF SCREENING FOR CERVIX CANCER

Barron, B. A., Columbia University, College of Physicians & Surgeons, Dept. of Obstetrics & Gynecology, *630 W. 168th St., New York, New York*, 10032, United States of America

Cancer of the uterine cervix contributes significantly to the total cancer morbidity and mortality among women in the United States. Cytologic screening using the Papanicolaou smear has become a widely accepted modality for detecting cervical neoplastic disease. The cost-effectiveness of Papanicolaou smear screening on an annual basis has been questioned. Recently, recommendations have been made for modifying current practices by increasing the interval between successive cytologic examinations among those women identified as being at 'low risk' of incidence. In no instance have the sequelae of such proposed changes been examined in terms of expected changes in incidence, survival and mortality for cancer of the cervix.

The natural history of cervical neoplastic disease has been described by us and other investigators. Several cytologically defined lesions are thought to be precursors of invasive cancer of the cervix and there is wide acceptance that carcinoma-in-situ is antecedent to invasive disease. This lesion is potentially 100% curable and will, if untreated, progress to invasive cancer in the majority of cases. The transition times and probabilities of the stages of cervical neoplastic disease have been presented previously. Using these data together with age-specific incidence rates currently available from a variety of sources and available estimates of incidence, the studies proposed here will generate estimates of the incidence, survival and mortality for cervix cancer among defined populations exposed to specified cytologic screening regimens.

BIBLIOGRAPHIC REFERENCES: Barron, B.A., Cahill, M.C., and Richart, R.M. (1978) A statistical model of the natural history of carcinoma-in-situ of the uterine cervix. Gynecologic Oncology Vol. 6, 196-205. Barron, B.A. (1978) Estrogen and endometrial cancer: an unresolved issue. Comprehensive Therapy Vol. 4,3, 45-51.

335. EXPANSION OF MARYLAND CERVICAL CANCER SCREENING PROGRAM

Sawada, E. A., State Dept. of Health, *301 W. Preston St., Baltimore, Maryland*, 21201, United States of America

The objective of this project is to reduce the incidence, morbidity, and mortality of carcinoma of the cervix among Maryland women. In this second year we changed our methods for achieving this objective. Rather than have 5 counties provide this service we have encouraged every county to submit a proposal. There are currently 12 counties funded, with 3 more projects to be funded shortly, including Baltimore City. The Central Office will conduct screening, utilizing portable equipment and nurse consultants. This second year 20,000 Pap tests will be performed, with the target population continuing to be women over the age of 16 who have never had a Pap test or have not had one in at least a year.

336. SCREENING FOR THE EARLY DETECTION OF CANCER

Albert, A. E., Freedman, M., Schwartz, M., Plough, A., Cupples, A., Boston University, School of Liberal Arts, Dept. of Mathematics, *755 Commonwealth Ave., Charles River Campus, Boston, Massachusetts*, 02215, United States of America

We propose to develop a second generation mathematical model and computer systems program dealing with the impact of screening on the natural history of and mortality from breast and cervical cancer. The program objectives are: 1) To extend an existing first generation model, 2) to develop statistical estimation techniques in order to furnish the inputs necessary for the exercise of the model described above; 3) to design screening programs so that data suitable for the goals of 2) are obtainable; and 4) to apply these methods to existing bodies of data such as the British Columbia Cervical Cancer Screening Projects and the Breast Cancer Demonstration Project in order to obtain insights into the natural history of cervical and breast cancer. In turn, these insights will allow us to design screening programs which utilize limited resources efficiently.

337. CERVICAL CANCER SCREENING PROGRAM DATA SUPPORT PROJECT

Peterson, R., Evaluation Technologies Inc., *2020 N. 14th St., Suite 620, Arlington, Virginia*, 22201, United States of America

OBJECTIVE: Provide the computerized data management system for the collection, editing, organization, storage, and retrieval of all pertinent data gathered in the Cervical Cancer Screening Program.

338. IMPLEMENTATION OF CERVICAL CANCER SCREENING PROGRAM

Kwalick, D. S., State Dept. of Health, *135 W. Hanover St., Trenton, New Jersey*, 08618, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

339. SCREENING FOR EARLY ENDOMETRIAL CANCERS

Koss, L. G., Montefiore Hospital & Medical Center, *111 E. 210th St., Bronx, New York*, 10467, United States of America

OBJECTIVE: To identify a group of women over age 45 and up to 70 years of age that regularly attend the clinic of the Contractor's institution. The number of such women shall have been determined with biostatistical consultation in order to be adequate for testing the goal. In order to carry out the program successfully, the Contractor will be expected to meet the following requirements: ability to demonstrate that this population has in the past indicated a responsiveness for regular recall and follow-up, acceptable methodology for obtaining endometrial specimens, and availability of biostatistical and computer support.

B. STUDIES ON THE DEVELOPMENT OF AUTOMATED CYTOLOGY SCREENING METHODS

340. FLOW-CYTOMETRIC PRESCREENING FOR CERVICAL CANCER DETECTION

Linden, W. A., Baisch, H., Scholz, K., Universitat Hamburg, Institut fur Biophysik und Strahlenbiologie, *Martinistrasse 52, 2000 Hamburg 20, Federal Republic of Germany*

OBJECTIVE: To develop an automatic cytophotometric prescreening method for detection of cervical cancer.

APPROACH: Cell suspensions from cervical smears are analyzed by flow cytometry (FCM). The cellular DNA is stained with 4'-6-diamidino-2-phenylindol (DAPI) and the protein with sulfur-rhodamine (SR 101). The analysis is based upon the increased DNA content of malignant cells and the different nuclear/cytoplasmic ratio. Each two-parameter FCM measurement is evaluated mathematically to discriminate between normal and suspicious samples.

PROGRESS: Our previous investigations have shown that measurement of DNA content alone is not sufficient (Linden W.A., Ochlich K., Baisch H., Scholz K.-U., Mauss H.-J., Stegner H.-E., Joshi D.S., Wu C.T., Koprowska I., Nicolini C., Flow cytometric prescreening of cervical smears. J. Histochem. Cytochem. 27, 529-535 (1979)). Comparing the FCM results with the cytologic diagnoses after Papanicolaou staining we obtained 26% false positives admitting 11% false negatives. In the present study a field test with two-parameter FCM measurements is being conducted. Criteria for mathematical analysis of histograms are evaluated to identify suspicious subpopulations.

341. BIOPEPR - SCREENING OF CERVICAL SMEARS

Van de Walle, R. T., Vooys, G. P., Zahniser, D., Oud, P., Raaymakers, M., Katholieke Universiteit Nijmegen, Physics Lab., High Energy Nuclear Physics Section, *Toernooiveld, 6525 ED Nijmegen, Netherlands*

OBJECTIVE: To develop a fast (approximately 100 smears/hr) apparatus for pre-screening of cervical smears with a false alarm rate of 10 percent or less and a missed positive rate of 1 percent or less.

APPROACH: A cathode-ray tube scanner looking at (enlarged) pictures of smear-fields, derived from an instrument developed in high energy physics for the analyses of bubble chamber film; development of special preparation and staining techniques in order to obtain smears suitable for fully automatic scanning.

PROGRESS: In a sample of approximately 200 smears measured at speeds between 120-180 smears/hr and with a missed positive rate of less than 1 percent approximately, a false alarm rate of approximately 18 percent was obtained (results reported at the 6th Int. Conference on Automated Cytology - Elmau, April 1978). Field test on a sample from more than 5,000 smears is now in progress.

342. AUTOMATION OF PRESCREENING PROCEDURES FOR CERVICAL CARCINOMA AND HEMATOLOGICAL DISORDERS WITH TV ANALYSIS

Ploem, J. S., Al, I., vanIngen, E. M., Leyte, L., Ploem, J. J., Vrolijk, J., Tanke, H. J., vanDriel, A. J., Koper, C. J., Verwoerd, N. P., Wielenga, G., Rijksuniversiteit te Leiden, Sylvius Labs., Dept. of Histochemistry & Cytochemistry, *Wassenaarseweg 72, P.O. Box 9503, 2300 RA Leyden, Netherlands*

The objective of the research is a rapid automated screening procedure for cervical carcinoma and premalignant lesions of the cervix. At first, a semi-automated investigation was performed on a large clinical material consisting of 772 cervical smears. These smears were visually screened for cells with a visually expected high DNA content. The fluorescence of these cell nuclei was subsequently measured. It appeared that about 10% of the negative smears contained cells with a DNA content of more than 5C (false positives). In the positive material (moderate/severe dysplasia and more serious lesions), 95% of the smears contained cells with such a high DNA content (5% false negatives). This criterion thus seemed suitable for use as one of the prescreening criteria. We found an increased contrast of nuclear chromatin structure a second useful criterion in a prescreening program for cervical cancer. It was possible to implement artifact rejection procedures in our television analysis computer (LEYTAS) which resulted in an efficient elimination of artifacts. The mean number of non-rejected artifacts on plus or minus 20,000 analyzed objects was only 5. A total of 86 negatives and 139 postives were analyzed with LEYTAS. The whole screening procedure is carried out without intervention of the operator, meaning that autofocus, transportation of the stage, detection of objects, rejection of artifacts, and accumulation of relevant data such as the location of detected non-rejected objects are fully automated. At the end of the procedure the detected non-rejected objects can be visualized in the preparation as well as on TV screen. By visual judgement the artifacts are then separated from the single cells, which can be further divided into negative, suspicious and positive. Further implementaton of criteria concerning chromatin structure is at present being developed. The result of the 225 preparations that were screened with LEYTAS on increased DNA content and chromatin contrast resulted in a false negative ratio of about 2%.

343. AUTOMATION OF CANCER CYTOLOGY FOR SCREENING OF UTERINE CERVICAL CARCINOMA (CYBEST SYSTEM)

Tanaka, N., Ikeda, H., Ueno, T., Watanabe, S., Kashida, R., Chiba Cancer Center Research Inst., Dept. of Pathology, *666-2, Nitona-Cho, Chiba 280, Chiba, Japan*

OBJECTIVE: Prescreening of uterine cervical cancer by an automated cytoscreening system applying mass screening.

APPROACH: Based on fundamental studies initiated in 1967, we developed the automatic prescreening system (CYBEST - Cytobiological Electronic Screening System) in 1972, using the pattern recognition method. The slide smear sample stained with PAP stain serves as the specimen. This system has 2 stages of flying spot scanning: 4 micron spot coarse scan and 1 micron spot fine resolution, which is automatically activated. Final cytological assessment is printed out under 3 different categories: normal, suspicious and reject (sample inadequate). Up to the final assessment, 5-6 minutes is required per slide.

PROGRESS: Repeating the field tests using many samples, including malignant cases, the software program on diagnostic algorithm has improved. False negative rate was 0-3%, including sampling error, and the false positive rate of 29-38% can be maintained. To reduce the false positive rate to about 20% is our present project goal. The system is now experimentally applied in the practical mass screening of over 3,000 females.

344. CYTOPHOTOMETRY IN DETECTING RECURRENCE OF CERVICAL CARCINOMA (HUMAN)

Okagaki, T., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Therapeutic Radiology, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

This is part of a broader project. A summary of this subproject is not available.

345. AUTOMATED CANCER CELL DIAGNOSIS BY THE TICAS METHOD

Wied, G. L., Bartels, P. H., Bibbo, M., Sychra, J., Taylor, J., University of Chicago, Pritzker School of Medicine, Dept. of Obstetrics & Gynecology, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

High-resolution microphotometric scanning methods enable the objective characterization and automated recognition of epithelial cells with excellent reliability. The extensive computer programs of the TICAS system will now be applied to the next higher level, to the diagnostic assessment of the entire cytologic sample from a given patient. Patient sample profiles will be established and the best profile features that identify a diagnostic condition determined. Diagnostic clues comprise the cellular composition of the sample and the state and degree of cellular atypia. A thorough investigation will be made of recently detected differences between cells of normal cell types, cells from patients with dysplasia, and cells from patients with carcinoma in situ, since these observations may have a portentous impact on the detection of cervical cancer. Sample profiles from patients with dysplasia will be examined for homogeneity of this diagnostic entity.

346. DEVELOPMENT OF AUTOMATED CELL RECOGNITION SYSTEM

Wied, G. L., University of Chicago, Pritzker School of Medicine, Dept. of Pathology, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

OBJECTIVES: Feasibility study on optimizing selection of wavelengths for three-color scanning of Papanicolaou-stained gynecologic specimens. Supply NCI with industry-compatible magnetic tapes containing digitized raw image and edited images of all cells studied under this contract accompanied by identifying and diagnostic information similarly recorded on an ongoing basis and by photomicrographs. Replacement of the current green filter in the new three-color scanning system by an interference filter id. Brief study using the three-color system in which only unequivocal gynecologic cytopathology specimens are used as the 'learning' data base.

C. IMMUNODIAGNOSTIC AND PROGNOSTIC STUDIES

347. OCCURRENCE OF PRE-NEOPLASTIC STAGES OF CERVICAL CARCINOMA IN PATIENTS WITH CHRONIC CERVICITIS

van de Linde, A. W., Kater, L., Streefkerk, M., State University Hospital, Dept. of Internal Medicine & Pathology, *Catharijnesingel 101, Utrecht, Netherlands*

Aim of the study is to evaluate whether pre-neoplastic stages of cervical carcinoma in patients with chronic cervicitis can be detected by immunological methods. We therefore are searching for the occurrence of tumor specific antigens for cervical carcinoma on cervical epithelium of patients with chronic cervicitis.

For the investigation of changes in antigenic structure, different immunological test systems are set up. Blood from patients with invasive cervical carcinoma is used to test reactivity to cultured cervical carcinoma cells or antigen preparations from fresh and cultured carcinoma cells.

If positive reaction with cervical carcinoma patients are found, one or more test systems in material from patients with carcinoma in situ, dysplasia and chronic cervicitis will be used in order to investigate the reactivity of serum and leukocytes from these patients to antigenic determinants of cervical carcinoma.

The techniques applied are: the membrane-immunofluorescence assay on cultured cervical carcinoma cells, the lymphocyte stimulation assay, the leukocyte migration inhibition assay and the leukocyte adherence inhibition assay.

In the membrane immunofluorescence assay, 82% of the sera of 62 patients show reactivity to cultured cervical carcinoma cells. Positive reactions are also obtained with 50% of the sera of 40 normal, healthy young donors. However, when absorbed with tonsil lymphocytes from 10 different donors, patient sera remain positive, while control sera result in negative staining. In the test systems based on a cellular reaction we use 2 kinds of tumor antigens: extracts from fresh tumors and serum-free culture supernatants from cultured human cervical carcinoma cells. Whole extracts as well as fractionated extracts give irreproducible results in all three test systems, probably due to the fact that these antigen extracts are mixtures of different kinds of peptides.

When supernatants from cultured cervical carcinoma cells are used, positive reactivity with leukocytes of patients is detected especially in the leukocyte adherence inhibition assay (LAI). To date all patients tested in LAI have been strongly positive while control donors have been negative.

348. ASSOCIATION STUDIES OF HUMAN LEUCOCYTE ANTIGENIC (HLA) AND OTHER MARKERS IN CERVIX CANCER

Undevia, J. V., Bagwe, A., Balavat, P. L., Kirk, R. L., Cancer Research Inst., Epidemiology Div., *Dr. Ernest Borges Marg, c/o Tata Memorial Ctr., Bombay 400012, Maharashtra, India*

HLA is being studied in a variety of malignant and non-malignant diseases throughout the world. Cervix cancer is very common among Indian women. Several factors such as herpes type virus, other environmental factors, marital history, obstetric experience, hormonal status, age at first delivery, genetic status, etc. have been implicated in the etiology of cervix cancer. Adenocarcinoma of the uterus has been found to run in some families. Dostal and Mayr (Vienna, Austria) have investigated HLA antigens in cervix cancer and as preliminary observations reported an increased frequency of BW-15 or HLA-B12 in cervix cancer patients in comparison with controls. HLA associations with cervix cancer will be studied in a large sample (200) along with matched controls. Analysis of red cell and plasma antigens and of enzyme variations is part of this division's ongoing program of genetic marker studies in cancer sites in selected populations. These studies will be undertaken simultaneously with HLA studies in cervical cancer cases. Forty cancer cases and an equal number of controls have been investigated so far.

349. DEVELOPMENT OF IMMUNODIAGNOSTIC TESTS FOR CANCER

Ibrahim, A. N., Georgia State University, School of Arts & Sciences, Dept. of Biology, *33 Gilmer St. S.E., Atlanta, Georgia,* 30303, United States of America

OBJECTIVES: Increase the specificity and the sensitivity of an immunodiagnostic test for cervical and head and neck cancer. Purify the tumor associated antigens. Prepare specific antisera against these antigens. Periodically monitor the test by testing aliquots of sera from the same serum panel provided by NCI. An appropriate clinical evaluation of the immunodiagnostic test shall be done when the test is refined to the satisfaction of the Immunodiagnosis Program.

350. DIAGNOSTIC APPLICATIONS OF HUMAN TUMOR ANTIGENS

Alexander, E. R., University of Washington, School of Public Health & Community Medicine, Dept. of Epidemiology, *4000 15th Ave. N.E., Seattle, Washington,* 98105, United States of America

OBJECTIVE: Develop and evaluate immunodiagnostic methods for recognizing epidermoid cervical cancer antigen and antibody by: purifying and characterizing the epidermoid cervical cancer antigen described in the proposal; developing quantitative radioimmunoassays for this antigen and related antibody; seeking methods for recognitions of this antigen in cells and/or tumors; studying distribution of the antigen or related antibody in the sera of selected populations of cancer patients, patients with cervicitis, and matched controls. When test appears to discriminate between cancer patients and controls, test a coded panel of serum specimens to be provided by NCI and determine the utility of a test in early diagnosis in an ongoing prospective study.

351. ESTABLISHMENT OF AN IMMUNOLOGICAL SERUM TEST FOR OVARIAN CANCER

Berger, E. G., Verdon, B., University of Bern, Med. Chem. Institut, *CH3000 Bern 9, Switzerland*

OBJECTIVE: Diagnosis and follow-up of ovarian cancer by serum galactosyltransferase measurements by ELISA.

APPROACH: Since the structure of human milk galactosyltransferase (EC 2.4.1.22) appears to be very similar to an enzyme present in malignant effusions, purified human milk galactosyltransferase is used to elicit specific antisera in rabbits. A competitive ELISA for antigen determination is developed by applying a phosphatase-galactosyltransferase conjugate. The sensitivity of the assay is in the order of magnitude of nanograms/ml.

PROGRESS: The purification procedure of the milk antigen outlined by Gerber et al. was extended to exclude contaminants present in trace amounts but strongly immunogenic. Monospecific antibodies were prepared on a galactosyltransferase-agarose column and used for immunohistochemical and cytochemical localization of antigen in HeLa cells. Further work is aimed at correlating enzyme activity with immunoreactive protein in sera and body fluids.

352. IMMUNODIAGNOSIS OF HUMAN OVARIAN CANCER

Urbach, G. I., Wellesley Hospital, Dept. of Obstetrics & Gynecology Research, *160 Wellesley St. E., Bruce Wing/Room 765, Toronto, Ontario,* M4W 1J3, Canada

OBJECTIVE: Ovarian cancer is an occult neoplasm which usually remains undetected until the curative stage has passed. We have been investigating ovarian tumor-associated antigen NB/70K with the intention of developing a radioimmunoassay capable of detecting tumor antigen in plasma before clinical signs of disease are apparent.

APPROACH: We have purified human ovarian tumor-associated antigen NB/70K from surgical specimens of ovarian epithelial tumors. NB/70K appears to be a tumor-associated antigen which has no cross-reactivity with carcinoembryonic antigen and which has an apparent molecular weight (as estimated by SDS acrylamide gel electrophoresis) of approximately 60,000-70,000 daltons. We propose to develop a radioimmunoassay sensitive enough to detect NB/70K in plasma. Once the assay has been developed, we will examine plasma samples from groups of patients with ovarian tumors, non-ovarian tumors, benign gynecological disease, and benign non-gynecological disease as well as from a normal control population so that the selectivity and specificity of the assay can be determined. We also propose to investigate the use of the assay for staging and monitoring the progression of disease in patients being treated for ovarian cancer.

353. IMMUNE ASSAYS FOR ENZYMES AND ISOZYMES IN CANCER

Shaper, J. H., Johns Hopkins University, School of Medicine, Dept. of Oncology, *725 N. Wolfe St., Baltimore, Maryland,* 21205, United States of America

OBJECTIVES: Evaluate the immunodiagnostic significance of serum levels of UDP-galactosyltransferase in human breast and ovarian carcinoma. Specifically: develop a sensitive and highly specific radioimmunoassay for human serum galactosyltransferase, systematically examining the efficacy of antiserum produced from bovine milk, normal human serum,and human ascitic fluid; determine if a cancer-associated isoenzyme of galactosyltransferase, chemically similar to the isoenzyme reported in serum, is present in human ascitic fluid; assess the immunological cross-reactivity or relatedness of galactosyltransferase isolated from the three sources listed above; and once the radioimmunoassay has been developed, conduct, after consultation with the Projcct Officer, a clinical study correlating serum UDP-galactosyltransferase levels with tumor burden, disease state, and response to therapy.

354. ANTIGENS OF HUMAN OVARIAN TUMORS

Lloyd, K. O., Old, L. J., Lewis, J. L., Welander, C. W., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

Ovarian cancer is second only to breast cancer as the most common cause of death from gynecological malignancy in women in this country. The principal objective of this project is to identify antigens or markers of ovarian tumors which can be used in an immunodiagnostic assay for the detection of early ovarian cancer. Xenogeneic sera will be used to identify (1) antigens in extracts of ovarian tumors and (2) cell surface and shed antigens of cultured ovarian tumor cell lines. Using rabbit antisera we have already identified two antigens (OvC-1 and OvC-2) present in ovarian tumors but not in normal ovaries. Both these antigens are present in amniotic fluid which is a convenient source of material for isolation of the antigens. OvC-1 is a new pregnancy-associated antigen. OvC-2 is a new oncofetal antigen and is found in a fetal intestine as well as in ovarian tumors. The development of sensitive assays (e.g. radioimmunoassays) capable of detecting these antigens in serum or plasma will enable us to determine their possible usefulness for the immunodiagnosis of ovarian cancer. Cultured ovarian tumor cells will be used in attempts to identify new antigens not previously identified when tumor extracts were used. Components shed from cultured ovarian tumor cells will also be studied. Antisera to the cultured cells and their released components will be raised in rabbits and monoclonal antibodies will be produced using the procedure of Kohler and Milstein. The specificity of the antisera will be studied by serological techniques using binding or adherence assays and by radioimmunoprecipitation. New antigens showing ovarian tumor specificity will be examined for their possible use in the early detection of ovarian cancer.

355. IMMUNODIAGNOSIS FOR EARLY DETECTION OF OVARIAN CANCER

Stolbach, L. L., Tufts University, Boston Campus, School of Medicine, Dept. of Medicine, *136 Harrison Ave., Boston, Massachusetts*, 02111, United States of America

OBJECTIVE: Establish an immunodiagnostic method of identifying the existence of ovarian cancer at an early stage of the disease and for serial monitoring of patients with ovarian cancer so that treatment can be more effective. Specifically, the Contractor will have available an immunologically oriented laboratory capable of recreating, identifying, and purifying antigens and creating antigens and creating antisera; he will have radioimmunoassay capability in order to perform large numbers of tests on patients; he will have access to patients with carcinoma and will locate, identify, and have access to a population cohort at high risk for ovarian cancer, including expected laparotomy for suspicion of ovarian cancer.

356. CLINICAL SUPPORT STUDIES

Bagshawe, K. D., Charing Cross Hospital, Dept. of Medical Oncology, *Fulham Palace Rd., London, W6 8RF, England, United Kingdom*

These studies comprise 3 more or less unrelated topics.

OBJECTIVES: 1. To determine whether cryopreservation of autologous marrow can be used to improve the responses of myelosuppressed patients following prolonged chemotherapy. 2. To determine whether the leucocyte adherence inhibition test is of diagnostic value in colonic carcinoma. 3. To determine whether antibodies in the Ii blood group system are of use as tumor markers.

APPROACH: Project 1: Patients undergoing intensive chemotherapy for solid tumors have marrow taken before significant amounts of chemotherapy have been given and cryopreserved in a conventional manner. The marrow will be returned to the patient after a standard number of intensive courses of chemotherapy and the extent of myelosuppression following subsequent courses of chemotherapy will then be determined, using appropriate controls. Project 2: Leucocyte adherence inhibition test using microtrays and cell counter supernate will be applied using saline extracts of normal and malignant tissues. Project 3: Evidence for anti-i antibodies in a small number of patients with choriocarcinoma has been presented. The presence of anti-i has been observed in various other disease states and is regarded as pathological. Evidence for the presence of anti-i in the sera of a larger group of patients with invasive mole and choriocarcinoma will be undertaken at appropriate temperatures.

357. IMMUNODIAGNOSIS OF GYNECOLOGICAL MALIGNANCIES

Kauppila, A., Oulu University Central Hospital, Dept. of Obstetrics & Gynecology, *Kajaanintie 51, 90220 Oulu 22, Finland*

OBJECTIVE: To evaluate the clinical value of carcinoembryogenic antigen (CEA) and carbocyanide dye-binding polyanion in the diagnosis of malignancies as well as in the follow-up of patients after treatments.

APPROACH: This investigation was started about two years ago and about 250 patients have been studied before, during and after treatment. CEA determinations have been made radioimmunologically (Reagents are supplied by F.Hoffman-LaRoche Diagnostica) and CPA photometrically.

PROGRESS: Preliminary results have been reported in the XIX Congress of Scand. Assoc. for Obstetricians and Gynecologists, Reykjavik, 1-4th June 1976. (Abstracts, p.49).

358. IMMUNE COMPLEXES AND SPECIFIC ANTISERA IN OVARIAN CANCER PATIENTS - A PROGNOSTIC INDEX AND THERAPY MONITOR (ABBREV)

Symonds, E. M., Baldwin, R. W., Clarke, A. G., Vasey, D., University of Nottingham, Cancer Research Campaign Lab., Dept. of Obstetrics & Gynaecology, *University Park, c/o City Hospital, Nottingham NG7 2RD, England, United Kingdom*

OBJECTIVE: To evaluate whether immunoassay of circulating tumor-associated products in ovarian and other gynecological cancers can be used for diagnostic purposes in monitoring tumor burden and assessing responses to therapy.

APPROACH: Screening tests of C1q precipitation for immune complexes using serum and ascites fluid. Immunotherapy trial comparing two treatment groups: 1. Surgery plus chemotherapy. 2. Surgery plus chemotherapy plus BCG immunotherapy.

PROGRESS: No elevation of immune complexes has been found to be associated with ovarian cancer using direct C1q, indirect C1q, indirect heat inactivated or Raji assays. Levels have been found to be raised in other gynecological tumors, e.g., carcinoma of the cervix, vulva and body of the uterus. The BCG immunotherapy trial is in progress.

Fourteen patients have been treated on a double-blind basis with BCG or placebo. Results so far do not indicate any alteration of prognosis with intraperitoneal BCG.

359. CIRCULATING IMMUNE COMPLEXES IN MALIGNANCY

Walker, L. C., Pookim, Y. L., Keen, J., Tucker, D. F., Imperial Cancer Research Fund, Laboratory for Immunological Markers in Cancer, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

As part of this laboratory's continuing interest in the possible prognostic value of circulating immune complex (CIC) measurement in malignancy, we have set up two assays for the routine determination of CIC levels. These are the C1q solid phase assay (C1qSPA) of Hay et al., (Clinical and Experimental Immunology, 1976, 24, 396) and a radioassay for IgC which is used to measure complexed IgG in solubilized polyethylene glycol (PEG) precipitates. The former test is based on the ability of immune complexes to bind to the first component of complement and the latter is a more specific assay than that of Digeon et al., (Journal of Immunological Methods, 1977, 16, 165) which was employed in previous investigations (see ICRF Scientific Report 1978 - report 240). These assays are also of use in identifying strongly positive sera for immune complex isolation and analysis, which in turn may provide clinically relevant information with respect to the nature of the complexed components.

Initially, we have restricted the scope of CIC evaluation to the selected malignancies detailed below. A) Non-lymphoid malignancy: In collaboration with Dr. Richard Begent and Kerry Chester at the Charing Cross Hospital, we are screening serial samples from patients with different malignancies in an attempt to correlate levels of CIC with established tumor markers; human chorionic gonadotropin (hCG) and alpha fetoprotein in malignant teratoma; hCG in choriocarcinoma. In conjunction, we are also examining sera from patients with ovarian cancer following a report (Poulter et al., Lancet, 1978, 2, 72) that CIC rise before clinical detection of relapse. B) Lymphoid malignancy: We are investigating the relationship between CIC levels, the serum factor T23 (report 235) and the course of disease in leukemia, Hodgkin's and non-Hodgkin's lymphoma. Following this, attempts will be made to define the nature of the components of the isolated immune complexes. Preliminary results indicate that the PEG assay detects more positives than the ClqSPA in all groups tested. At onset of disease, CIC were elevated in the majority of patients with acute myeloid leukemia (14/21) and acute myelomonocytic leukemia (7/9) but showed a lower incidence in acute lymphoblastic leukemia (3/8). (Text Abridged)

360. PROGNOSTIC VALUE OF SEQUENTIAL CEA ESTIMATIONS IN OVARIAN CANCER

Malkin, A., Kellen, J. A., Sunnybrook Hospital Medical Centre, Dept. of Clinical Biochemistry, *2075 Bayview Ave., Toronto, Ontario*, M4N 3M5, Canada

During the last two or three years, substantial data has accumulated indicating that in patients with colorectal cancer, lung cancer and breast cancer, the carcinoembryonic antigen (CEA) test has prognostic significance independent of stage as determined using standard clinical and diagnostic criteria. We have made similar preliminary observations in patients with ovarian cancer.

Aside from stage of disease, a number of other apparently independent variables such as histologic type, grade and amount of residual tumor after laparotomy all influence prognosis in ovarian cancer. The question arises whether the CEA test, determined either early post-operatively or sequentially thereafter, provides prognostic information independent of the foregoing variables and if so, to what extent it is useful as a prognostic indicator when compared with more conventional criteria.

In the design of clinical trials, care is taken to stratify patients before randomization into treatment arms to take account of factors which may introduce bias into the interpretation of results. While it may be utterly impractical to stratify for all known variables, that is, to assemble completely homogeneous populations for clinical studies, nevertheless, it is clear that these factors must be recognized and taken into consideration in drawing conclusions from the studies. The CEA test appears to have acquired prognostic significance for a number of solid tumors. We feel that this fact merits confirmation in ovarian cancer and its role in the design of clinical trials in this disease clearly established.

D. OTHER DIAGNOSTIC AND PROGNOSTIC STUDIES

361. IMFLAMMATORY INFILTRATION OF THE STROMA OF UTERINE CERVIX CANCER - HISTOLOGIC AND GEOGRAPHIC ASPECTS, PROGNOSIS (ABBREV)

Cardoso, V. M., Oliveira, A. M., Filho, P. L., Terra, P. L., Hospital Araujo Jorge da ACCG, *Rua 239 No. 181, c/o Setor Universitario, Goiania 74000, Goias, Brazil*

OBJECTIVE: To determine whether inflammatory infiltration of the stroma in cervical cancer has prognostic significance or if it correlates with histologic type and geographical influence.

We will study routine biopsy specimens, describing them with special emphasis on the inflammatory infiltrate and histologic type of cervical cancer. We will perform retrospective analyses. We will eventually compare survival, therapeutic response and some immunological aspects of each case. We hope to study 200 cases and review the literature to determine possible geographic influence.

362. CYTOLOGICAL FOLLOW-UP AND CLINICAL EVOLUTION IN THE EARLY STAGES OF CERVICAL DYSPLASIA

Schlaen, I., Freyre Hospital, Seccion Histopatologia, *Olive 1151, Mendoza 1670, 2000 Rosario, Argentina*

The objectives of this project are to study the controversial aspect of the potential evolution of dysplasias as they appear spontaneously, to investigate the influence of local factors introduced by the clinician for the purpose of control or treatment, and to validate the efficacy of cervical cytology as a means of control of the process in every case, establishing for all conized tissue the correlation between the verified histologic diagnosis and preceding cytological evaluation.

All files pertaining to a private cytology laboratory that services 8 gynecologic institutions will be reviewed. A selection will be made to include all cases with a follow-up of at least 3 consecutive cytologic exams and 6 months of control, excluding cases treated with conization immediately.

In all such selected cases, a review will be made of the clinical history in order to confirm all available information and to obtain precise information on possible incidental factors in the evolution, particularly biopsies, electrocoagulation or cryosurgery. (Translated)

363. CORRELATION BETWEEN CYTOLOGIC AND HISTOPATHOLOGIC STUDIES IN DYSPLASTIC AND NEOPLASTIC LESIONS OF THE UTERINE CERVIX

de Borges, R. J., Hospital Vargas, Departmento de Citologia, *San Jose, Caracas 101, Venezuela*

OBJECTIVE: The objective of this project has been to determine the degree of correlation between the cytologic evaluation and histopathologic diagnosis in the Hospital Universitario General of the city of Caracas. Since the establishment of the degree of correlation, cytodiagnosis has been used to determine the incidence of these lesions in the female population attending the various departments of the hospital.

APPROACH: As described in the previous paragraph, cytology and histopathology have been used to establish the statistical correlation between the two diagnostic methods. After determining the significance of the different cytologic changes, we have used this method to determine the incidence of dysplastic and neoplastic lesions of the uterine cervix.

PROGRESS: To date, we have studied 80,000 gynecologic cytological specimens. In 400 cases with alterations indicative of tumor (200) or dysplasia (200), a comparison was made with histopathologic diagnosis of these cases. Confirmation was obtained for 70% of the dysplasias and 95% of the lesions diagnosed as malignant in the first biopsy. Of the 80,000 cases studied, incidences of 2.8% dysplasias and of 1.4% malignant lesions were found with cytodiagnosis. We intend to continue adding cases to this study. (Translated)

364. COLPOSCOPY PROGRAM (HUMAN)

Stafl, A., University of Wisconsin, Madison Campus, Medical School, Dept. of Human Oncology, *307 N. Charles St., Madison, Wisconsin*, 53706, United States of America

This is part of a broader project. A summary of this subproject is not available.

365. THE NUCLEAR DIAMETER IN THE DIAGNOSIS OF ENDOMETRIAL ADENOCARCINOMA

Schlaen, I., Naves, A. E., Biso, T., Freyre Hospital, Seccion Histopatologia, *Olive 1151, Mendoza 1670, 2000 Rosario, Argentina*

Longitudinal and transversal diameters were measured in nuclei of 1,253 normal endometrial specimens and 1,213 endometrial adenocarcinoma specimens naturally exfoliated and collected in routine cervical smears. The determinations were performed blindly by two investigators who obtained the following mean diameters, respectively: longitudinal, 8.28 and 8.40 microns and diagonal, 6.44 and 6.64 microns for normal cells; longitudinal, 11.26 and 11.61 microns and diagonal, 8.97 and 8.87 microns for neoplastic cells.

Significant statistical differences in both populations were obtained, comparing the two diameters as independent variables. The feasibility of applying this simple method as a parameter in the cytological diagnosis of endometrial adenocarcinoma is currently under study.

366. DEVELOPMENT OF A CYTOMETRIC DATA BANK

Sadier, E., Guman, N., Hospital Mariano Castex, Servicio de Patologia, *Balcarce 900, 1650 San Martin, Buenos Aires, Argentina*

OBJECTIVE: To register cytometric data (nuclear and cytoplasmic diameters and size and percentage of micro- and macronucleoli) and cytomorphological data on histologic sections and cytologic specimens from approximately 600 malignant and benign tumors, hyperplasias, normal controls, etc.

This will provide data for an Automated Cellular Diagnostic System, and, during its development, will allow study of detailed classification of malignant tumors, relationship between tumors and preneoplastic atypias, oncogenic processes, etc.

METHOD: An ocular micrometer and immersion oil objective (1875 x) will be used in determining measurements and cytologic characteristics. The data will be processed electronically to obtain the arithmetic mean, standard deviation, and standard error and variance; they will be verified with the Student Test and Analysis of Variance. The results will be recorded on perforated cards.

PROGRESS: Data are complete on 1) colon adenomas, 2) endometrial hyperplasias, 3) cervical dysplasias and carcinomas in situ, 4) transitional cell carcinomas, papillomas and hyperplasias of the bladder, 5) basal hyperplasias and bronchial metaplasias, 6) non-Hodgkin's lymphomas, 7) nevi and melanomas, 8) canalicular breast carcinomas, 9) endometrial adenocarcinomas, 10) prostatic adenocarcinomas, 11) gestational endometrial hyperplasias, 12) colon adenocarcinomas, 13) gallbladder adenocarcinomas, 14) gastric adenocarcinomas, 15) atypias in chronic gastritis, 16) hepatomas, 17) skin basal cell epitheliomas, and 18) invasive squamous cell carcinomas of uterine cervix.

367. ASSESSMENT OF TECHNICS FOR ENDOMETRIAL CANCER DETECTION

Bibbo, M., Herbst, A. L., Reale, F. R., University of Chicago, Pritzker School of Medicine, Depts. of Obstetrics & Gynecology/Pathology, *5801 S. Ellis Ave., Chicago, Illinois,* 60637, United States of America

This study proposes to evaluate in the academic environment and in the community the relative efficacy of cytologic and microhistologic technics for the detection of endometrial cancer and its precursors. Three technics, namely the endometrial aspiration (vakutage), the endocervical aspiration and the routine vaginal, ectocervical and endocervical (VCE) cytologic smears, will be assessed. The present application is a continuation of an ongoing project at the University of Chicago which requires further studies in three main aspects: testing of the three technics on a large and statistically valid number of patients; assessment of the performance level of the three technics in a community setting (Outreach Program); and determination of the optimal fixation technic for endometrial samples which have to be transported for processing to a central laboratory. At the University of Chicago we will continue to study sample collections from outpatients who belong to the high risk group for endometrial cancer and its precursors. To test the performance level of the three technics in the community, two phases will be required: In a preparatory stage we will teach clinicians how to obtain good samples and provide guidelines for obtaining the best results possible. In the main stage of the study we will assess detection rates of endometrial cancer and its precursors on 400 patients employing a combination of the three technics. The optimal fixation technic for the endometrial aspirate will be investigated in the preparatory stage of the Outreach Program, utilizing various fixatives. The diagnostic accuracy of the methods of collection is to be assessed in an academic setting as well as in the community practice, and the hypothesis will be tested as to whether significant differences exist between the three methods and whether a combination of methods provides significantly better accuracy than any single method.

368. NATURAL HISTORY, PATHOGENESIS AND PROGNOSIS OF RARER OVARIAN TUMORS

Govan, A. D., Anderson, M. C., Gowing, N. F., Langley, F. A., Woodcock, A. S., Hill, S., Beilby, J. S., Fox, H., Royal Maternity Hospital, Pathological Laboratories, *Rottenrow, Glasgow G4 ONA, Scotland, United Kingdom*

The objective of the study is to establish reliable criteria for the diagnosis of the rarer types of ovarian tumor. At the same time there is a need to study the more common forms of ovarian malignancy and provide more precise histolocial criteria for their classification. To this end, material is collected from all parts of the United Kingdom and also from other countries; full clinical histories are obtained together with the results of laboratory and other investigations. A continuous follow-up of patients is maintained, the results of treatment are noted and an indication of prognosis obtained.

369. EVALUATION OF THE HUMAN TUMOR STEM CELL ASSAY AS A PREDICTOR FOR CLINICAL RESPONSE TO CHEMOTHERAPY

Von Hoff, D. D., University of Texas, Health Science Center at San Antonio, Medical School, Dept. of Medicine, *7703 Floyd Curl Dr., San Antonio, Texas,* 78284, United States of America

Advanced colorectal carcinoma, breast carcinoma, ovarian carcinoma, and malignant melanoma account for a significant number of deaths per year from cancer in the United States. A recent advance which would allow the correct choice of chemotherapy for an individual patient with one of these malignancies has been the development of the human tumor stem cell assays by Hamburger and Salmon. The overall objective of this proposal is to more completely develop and utilize the human tumor stem cell assay system as a tool to study both the basic and the clinical treatment of colorectal carcinomas, breast carcinoma, ovarian carcinoma, and malignant melanoma. More specifically this research will: 1) optimize conditions and determine specificity of growth of these four types of tumors in the stem cell system; 2) attempt to solve problems and difficulties noted in prior experience with the system; 3) determine if a correlation exists between in vitro drug sensitivity (as determined by the stem cell assay system) and clinical response to chemotherapy (as determined by a clinical trial). This methodical study should validate or invalidate the stem cell assay system as a predictor for clinical response to chemotherapy. In addition, it should define the utility of and the place for the system in the clinical care of patients with colorectal carcinoma, breast carcinoma, ovarian carcinoma, and malignant melanoma.

370. ESTABLISHMENT AND COMPARISON OF THE VALUE OF TWO ASSAY METHODS FOR CARCINOMA OF THE OVARY

Boesen, E. A., Corringham, R. E., Royal Free Hospital, Dept. of Oncology, *Pond St., Hampstead, London NW3 2QG, England, United Kingdom*

OBJECTIVE: The purpose of this study is to develop an in vitro method of assaying the sensitivity of carcinoma of the ovary to cytotoxic drugs and to compare this method with a tumor xenograft system in immune deprived mice.

APPROACH: Tumor cells will be obtained from ascites and effusions and from surgical specimens from patients with carcinoma of the ovary. In vitro method: After preparation the tumor cells will be cultured in soft agar. When cloning of the tumor cells has been successfully established further tumor cells from the same specimen of ascitic fluid will be incubated with various cytotoxic drugs prior to plating and the cloning ability of these tumor cells assessed. The results would be correlated with the response to cytotoxic drugs observed in vivo. Assessment will be repeated during the clinical course of the disease. Xenograft method: Tumor cells from the same sample will be implanted in immune deprived mice and an assessment made of the sensitivity to cytotoxic drugs. A comparison between the two methods can then be made.

371. HISTAMINASE AS A BIOCHEMICAL MARKER FOR HUMAN CANCER

Lin, C., Stolbach, L. L., Tufts University, Boston Campus, School of Medicine, Dept. of Medicine, *136 Harrison Ave., Boston, Massachusetts,* 02111, United States of America

Research from our own and other laboratories has established an association of increased histaminase with a number of human cancers. Based on this and the fact that this enzyme is produced at a very high level in placenta and at very low levels in most normal tissues, work has been done in our laboratory to establish histaminase as an 'onco-placental' enzyme by obtaining evidence for the biochemical and immunochemical identity of this enzyme from placentae, malignant effusion fluids and tumors. An affinity chromatography for the purification of this enzyme has been prepared, and specific immunohistochemical methods for the staining of this enzyme in tissues and cells have been developed in our laboratory. A survey conducted on a large number of malignant effusion fluids showed high (80%) incidence of elevated histaminase in cancers of the ovary, colon and stomach.

We now propose to evaluate further the potential of histaminase as a marker for human cancer by a combination of radioimmunoassay and immunohistochemical methods. A sensitive radioimmunoassay for histaminase will be developed and, with the immunohistochemical methods, the presence and quantitative variation of this enzyme as an antigen will be examined in sera, malignant effusion fluids, tumor cells and tumor tissues of cancers of various types and at various stages. The results will be correlated with the type and stage of the cancer and with the histopathological characteristics of the tumor. Biochemical and immunochemical studies of this enzyme will be carried out to obtain information pertinent to the development of a better technique for its detection and for understanding its significance in normal and tumor cells.

This study will be a major step toward the development of histaminase as a test for the detection and monitoring of cancer, and will have significance in the understanding of the basic biology of cancer.

372. EVALUATION OF CT BODY SCANNING IN ONCOLOGIC PATIENTS

Dunnick, N. R., Shawker, T., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, Clinical Center, Dept. of Diagnostic Radiology, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

OBJECTIVES: To compare CT scanning with other imaging modalities in the detection and follow-up of tumors. To extend our ability to image malignancies at presentation for staging purposes as well as to demonstrate followable disease.

METHODS EMPLOYED: CT is performed as a staging modality as well as at periodic follow-up intervals. Currently, patients with malignant lymphomas, ovarian carcinoma, malignant melanoma, testicular tumors, adrenal carcinomas, prostate carcinomas, oat cell carcinoma of the lung, and a variety of soft tissue sarcomas are being studied most intensively.

BIBLIOGRAPHIC REFERENCES: Dunnick NR, Schaner EG, Doppman JL, Strott CA, Gill JR and Javadpour N: CT in Adrenal Tumors. Am. J. Roentgenol. 132:43-46, 1979. Dunnick NR, Schaner EG and Doppman JL: Detection of Subcutaneous Metastases by CT. J. Comput. Assit. Tomogr. 2:275-279, 1978.

373. LYMPHOGRAPHY IN ONCOLOGIC PATIENTS

Dunnick, N. R., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, Clinical Center, Dept. of Diagnostic Radiology, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

OBJECTIVES: To evaluate the role of lymphography in comparison with other diagnostic modalities such as ultrasound and computer tomography in the staging and follow-up of patients with appropriate malignancies.

METHODS EMPLOYED: Bipedal lymphography is routinely performed on patients with a variety of malignancies, most specifically malignant lymphomas, testicular tumors, carcinoma of the prostate, carcinoma of the ovary, and Mycosis fungoides. Follow-up radiographs are performed at periodic intervals and an evaluation of the opacified retroperitoneal lymph nodes is made to assess disease progression.

MAJOR FINDINGS: Bipedal lymphograms performed on a series of 28 patients with carcinoma of the pancreas demonstrated extrapancreatic abnormalities in 4 patients. Indication of extrapancreatic disease may render these patients inoperable.

A method for delivering intralymphatic contrast material to patients who have undergone previous amputations making the usual dorsal pedal lymphatic route impossible was described.

Lymphography has been useful as one of several modalities in following patients with carcinoma of the prostate. It is limited in part by the relatively poor filling of retroperitoneal lymph nodes in older patients. Bipedal lymphography has thus far been quite useful in patients with testicular carcinoma, ovarian carcinoma, and malignant lymphomas. The better detail provided by lymphography is helpful in small sites of metastatic disease. Extranodal disease is more easily detected by computer tomography. Bulky disease can usually be readily identified by either method.

374. HIGHLY SENSITIVE ASSAY SYSTEMS FOR EARLY DETECTION OF OVARIAN CANCER

Lloyd, K. O., Sloan Kettering Inst. for Cancer Research, Human Cancer Serology Laboratory, *410 E. 68th St., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

375. CARCINO-PLACENTAL ALKALINE PHOSPHATASE IN GYNECOLOGICAL TUMORS

Haije, W. G., Baggerman, L., Talerman, A., Meerwaldt, J. H., Driel, J. V., Rotterdamsch Radiotherapeutisch Instituut, Depts. of Clinical Chemistry/Radiotherapy, *Groene Hilledijk 301, Box 5201, 3075 EA Rotterdam, Netherlands*

OBJECTIVE: To assess the usefulness of a specific and sensitive determination of CPAP in diagnosis and follow-up of patients with gynecological tumors.

With a sensitive solid phase EIA, CPAP is determined in sera of well documented patients with gynecological tumors under treatment in our institute and in cooperating gynecology departments of general hospitals in Rotterdam.

Histology of the tumors and CPAP-content of tumor tissue, as well as the role of other TM's (CEA) are evaluated together with the CPAP serum values in a longitudinal study.

376. A PROSPECTIVE STUDY OF FECAL STEROIDS AND BACTERIA IN NORMAL PERSONS WHO DEVELOP CANCER OF THE LARGE BOWEL, BREAST AND ENDOMETRIUM

Hill, M. J., Meade, T. W., Rutishauser, I., Cummings, J., Central Public Health Lab., Bacterial Metabolism Research Laboratory, *Colindale Ave., London NW9 5DX, England, United Kingdom*

In a preliminary retrospective case-control study (Lancet, 1:535, 1975) it was shown that the combination of a high fecal bile acid concentration and the presence of certain clostridia in the faeces characterised large bowel cancer patients. The value of this combination in discriminating between large bowel cancer patients and controls will be tested prospectively in 10,000 persons aged 45-75. Other cancers will be added if the retrospective studies in hand indicate that it would be worthwhile.

377. PROGESTERONE-SPECIFIC PROTEIN IN HUMAN ENDOMETRIAL SECRETIONS

Richardson, G. S., Massachusetts General Hospital, Dept. of Gynecology, *32 Fruit St., Boston, Massachusetts,* 02114, United States of America

The summary for this project is under entry no. 265.

378. THE USE OF COMPUTED TOMOGRAPHIC SCANNING IN ONCOLOGY

Brenner, D. E., Aisner, J., Wic nik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Medical Oncology Section, *Baltimore, Maryland,* 21201, United States of America

The advent of the computed tomographic scan has opened the possibility of locating, biopsing, and sequentially analyzing masses in previously inaccessible areas. To assess this technique, we have devised projects to prospectively study the capabilities and drawbacks of this technology. Fourteen patients with advanced carcinoma of the cervix have been evaluated preoperatively with good correlation for the presence of retroperitoneal adenopathy. Biopsies under CT guidance have provided adequate tissue in 75% of 25 patients studied. Ovarian carcinomas are being studied prospectively with 92% predictive accuracy. Other studies include serial assessments of other tumors, particularly lung tumors, and tumor volume studies. Further patient entries will provide more meaningful data in all projects described.

379. CANCER OF THE HUMAN CERVIX UTERI - EFFICIENCY OF DETERMINATION OF DNA AND LYSINE IN AUTOMATIC GYNECOLOGICAL PRESCREENING

Herzog, R. E., Deutsche Forschungsgemeinschaft, *Kennedyallee 40, Me 126/28, D5300 Bonn-Bad Godesberg 1, Federal Republic of Germany*

OBECTIVE: During carcinogenesis of the human cervix uteri we have found a significantly higher amount of the basic amino acid Lysine heterochromatin. Therefore the content of Lysine may be a parameter of heterochromatin in the cell nucleus, and its efficiency in automatic gynecological prescreening will be evaluated.

APPROACH: Unselected smears were stained and cytophotometrically evaluated. The content of DNA and Lysine was determined and put in histograms. These were compared with cytological and histological findings.

PROGRESS: Preliminary results show that the determination of Lysine and DNA is, in respect to the differential diagnosis (inflammation, hormones, dysplasia, carcinoma in situ and invasive cancer), superior when compared to the determination of DNA only.

380. BIOPHYSICAL PROBES FOR MALIGNANT CELLS

Todd, P. W., Docherty, J. J., Pennsylvania State University, University Park Campus, School of Science, Dept. Microbiology, Cell Biology, Biochemistry & Biophysics, *211 Whitmore Lab., University Park, Pennsylvania, 16802*, United States of America

The summary for this project is under entry no. 106.

381. UTEROSIGMOIDOSTOMY - NEW PROCEDURE IN DOGS

Whitmore, W., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York, 10021*, United States of America

This is part of a broader project. A summary of this subproject is not available.

VII. THERAPY OF GYNECOLOGICAL CANCERS

A. THERAPY OF CERVICAL CARCINOMA

382. RADIOTHERAPEUTIC CONTROL - COMPARISON OF DIFFERENT TYPES OF FRACTIONATED DOSES IN DIFFERENT NEOPLASMS

Pescetto, G., Ragni, N., Caldana, P. L., Bentivoglio, G., Scarpati, D., Pilot, A., Universita degli Studi di Genova, Obstetric & Gynecology Unit, *Viale Benedetto 15 2, I16132 Genoa, Italy*

OBJECTIVES: Evaluation of cesiotherapy in the course of cervical and vaginal therapy and in the prevention and therapy of vaginal recurrences of endometrial and cervical cancers; demonstration of possible advantages in the treatment of some gynecological neoplasms with fractionated doses; evaluation of the collateral effects of cesiotherapy; follow-up of the patients treated and computerized analysis of the data obtained for the evaluation of the effects of different types of cesiotherapeutic treatment and of different radiosurgical combinations.

APPROACH: 1) Treatment of 17 cases of cervical cancer, 7 of whom will be treated with fractionated cesiotherapy before surgical treatment and the remaining 10 (5 plus 5) - with 2 different sources with different intensity of doses, using the two stocks of sources provided by 'Curietron.' 2) Treatment of 10 cases of endometrial cancer with intracavitary cesiotherapy before surgical treatement, 5 of whom will be treated with a single dose and the other 5 - with fractionated doses, followed by surgical treatment after 4 weeks. It will be possible to establish which treatment has the greatest chances of therapeutic success, with clinical and physical controls (lymphography, ultrasound, TAC). 3) A two-year treatment of 10 cases of vaginal cancer, 5 of whom will be treated with a single dose of cesiotherapy and 5 with fractionated cesiotherapy. A follow-up using clinical and bioptical controls for all the patients treated with this type of therapy is planned.

383. CLINICAL EVALUATION OF EFFECTS OF DIFFERENT FRACTIONATION REGIMES IN RADIOTHERAPY

Loasses, A., Banelli, E., Capua, A., Maurizi Enrici, E., Salsano, F., Tombolini, V., Vitturini, A., Universita degli Studi di Roma, Istituto Radiologia, *c/o Policlinico Umberto I, Rome, Italy*

(a) Cell-mediated immunitary implications of a two-fraction scheme of post-surgical radiotherapy in patients affected by breast cancer: 67 patients were treated from December 1976 to April 1979. Average age was 51; 83 percent were resected following the method of Halsted; stage percentages: I 6, II 51, III 43. Technique of treatment: irradiation of regional lymph nodes by a shielded direct field, 4 MeV x-rays, produced by Linac. A depth dose of 1800 rads was reached in two sucessive fractions of 900 rads each, separated by a 48-hour interval. The treatment was well-tolerated and symptomatic side-effects were minimal. Follow-up is in progress. Four cases of relapse in the non-irradiated chest wall were observed. Analysis of the time course of peripheral blood cells appears to show a very limited drop in lymphocytes and in granulocytes. An immunologic evaluation is in progress.

(b) Split-course versus continuous radiotherapy for carcinoma of the uterine cervix: The aim is to compare the effects of continuous versus split-course scheme of irradiation for stage III or II squamous cell carcinoma of the uterine cervix, by a randomized study. End-points are response/remission rate, morbidity of treatments, and survival rate. Dosage schedule: Arm A: continuous radiotherapy - 4000 rads in 5 weeks by 4 MeV Linac x-rays, followed by intracavitary treatment with Ir-192. Arm B: split-course scheme: two fractions 850 rads each, 4 MeV Linac x-rays, separated by a 48-hour interval, followed by intracavitary treatment with Ir-192 after three weeks. Sixteen patients have been entered (12 in arm A, 4 in arm B). Split-course therapy was well tolerated by all 4 patients who showed complete remission. Six of twelve patients treated by conventional fractionation showed partial remission, and three of six after full remission developed a central relapse.

384. RADIOTHERAPY OF CANCER OF THE BLADDER, BRONCHUS, AND CERVICAL UTERI IN COMBINATION WITH RADIOSENSITIZING DRUGS

Rimondi, C., Busutti, L., Corrado, F., Fasano, E., Pazzaglia, G., Stecchi, V., M. Malpighi Hospital, Dept. of Radiotherapy, *Via Albertoni N. 15, 40138 Bologna, Italy*

A randomized clinical trial with misonidazole, a drug used for specific radiosensitization of hypoxic cells of tumors, in combination with daily multifraction radiotherapy (DMF) began in 1979 and included patients with 1) transitional bladder carcinoma, stage T3 NX MO, 2) non-oat cell bronchial carcinoma, non-resectable, 3) carcinoma of the cervix uteri, stage III. To test: the local and general tolerance of misonidazole in combination with DMF radiotherapy, particularly neurotoxicity; the immediate response of the tumor, evaluated as tumor mass volume reduction; the length of local tumor control, the quality of life and the survival of patients. For each side, patients were at random assigned to a study or to a control group. Study group patients were administered misonidazole every day, 650-800 mg/sq. m., 3 hours before the first session of radiotherapy, 1Gy 3 times every day with an interval of 4 hours between sessions, for 3-3 1/2 weeks. Control group patients received placebo instead of misonidazole; radiotherapy was administered following the same scheme. On the whole, 20 patients from the study group and 18 from the control group have been evaluated. The local tolerance to radiation treatment alone or in conjunction with misondazole was good, without significant differences between groups. 11/20 patients treated with misonidazole showed toxic symptoms (rash 1 p., oral mucositis 1 p., ototoxicity 1 p., sensorial peripheric neuropathy 6 pts.) which appeared 2-3 weeks after the beginning of treatment and persisted for 4-15 weeks. For all neoplastic sites tumor shrinkage was more frequent and larger in the misonidazole plus RT group than in the placebo plus RT group. A study of drug concentration in blood and in normal and neoplastic tissues in bladder carcinoma patients after total cystectomy has begun.

385. TREATMENT OF CERVICO-UTERINE CANCER WITH INTRAUTERINE HIGH-YIELD RADIATION

Garcia Sainz, G., Armendariz, C., Vazquez Curiel, A., Rodriguez, C., Instituto Mexicano del Seguro Social, *Av. Cuauhtemoc No. 330, c/o Hsp. Oncol.-Ctr. Med. Nac., Mexico City 7, Distrito Fed., Mexico*

OBJECTIVES: To evaluate therapeutic results and tolerance to treatment of cervicouterine carcinoma with the Cathetron, in comparison with results obtained using the established treatment of the Hospital de Oncologia which utilizes radium combined with external radiotherapy. To determine whether the new method may be substituted for the old one in light of such practical advantages as greater radiological protection of personnel, treatment on an out-patient basis and consequent savings in hospital days, and strict adherence to the treatment schedule.

In this controlled clinical trial the null hypothesis will be evaluated since, by definition, the new treatment is designed to satisfy conditions of isoeffectivity. If the null hypothesis is not rejected by this study it may be concluded that the new treatment is equivalent to the old in therapeutic effect and clinicopathologic tolerance. In that case it may be the treatment of choice because of the advantages in radiologic protection and savings in hospital days.

Patients with epidermoid cervico-uterine carcinoma will be accepted to the study with the following exceptions: a) Patients who have had prior therapy. b) Patients over 70 years of age. c)

Pregnant patients. d) Patients without an IMSS courtesy card. e) Patients who do not meet our criteria.

Patients who are accepted are randomized with stratification by clinical stage and assigned to treatment utilizing the Cathetron or the Hospital de Oncologia technique. Randomization is performed using tables with random numbers as published by Hill. A minimum of 300 patients will be assigned to each treatment in order to include at least 60 patients from each clinical stage in the study.

The following parameters will be analyzed: a) Interval free of tumoral activity based on initiation of treatment. b) Survival free of tumoral activity. c) Survival with tumoral activity. d) Proctitis. e) Cystitis. f) Leukopenia. g) Bone necrosis. (Translated)

386. A PHASE I CLINICAL TRIAL OF RADIATION SENSITIZERS AND A STUDY OF SOME OTHER THERAPEUTIC FACTORS

Thomas, G. M., Bush, R. S., Cummings, B. J., Dembo, A. J., Harwood, A. R., Hill, R. P., Rauth, A. M., Rider, W. D., Whitmore, G. F., Ontario Cancer Inst., Dept. of Radiation Oncology, *500 Sherbourne St., Toronto, Ontario,* M4X 1K9, Canada

OBJECTIVE: This is a phase I clinical and pharmacological investigation of two drugs, metronidazole and misonidazole. These drugs have potential use in the clinical setting as hypoxic cell radiation sensitizers. As such they may improve local control and cure with radiation of patients with carcinomas.

Our objective is to document and quantitate the types of acute toxicities associated with the administration of these drugs to patients receiving conventional daily fractionated radiation therapy to the pelvis in patients with carcinoma of the cervix and to the head and neck in patients with carcinomas of the head and neck.

APPROACH: Groups of patients are being studied at escalating levels of daily drug dosage. This will enable us to determine the maximum daily drug dosage which can be safely administered to such patients. It will also allow us to determine whether further trials to measure the therapeutic efficacy of these agents are justified.

Detailed pharmacokinetic studies using high pressure liquid chromatography are being performed to enable correlation of acute toxicities with plasma and urine drug levels.

387. PI MESON RADIOTHERAPY OF UTERINE CERVIX CARCINOMA (HUMAN)

Kligerman, M. M., University of New Mexico, School of Medicine, Dept. of Radiology, *University Hill N.E., Albuquerque, New Mexico,* 87131, United States of America

This is part of a broader project. A summary of this subproject is not available.

388. SURGICAL RESCUE IN THE FAILURE OF IRRADIATION IN THE TREATMENT OF CERVICOUTERINE CANCER

Jimenez Medina, J., Alert, J., Fleites, G., Gomez, E., Diaz, D., Instituto de Oncologia y Radiobiologia, Departamento de Radioterapia, *Calle 29 y E Vedado, Havana 4, Cuba*

OBJECTIVE: To treat patients with active cervical cancer in whom treatment with ionizing radiation has failed.

METHOD: Surgery: a) Wertheim-Meigs operation; b) pelvic exenteration. Patients are originally clinical stages I-II, A and B, or III (TNM).

389. URINARY TRACT DYSFUNCTION IN WOMEN AFTER RADICAL HYSTERECTOMY AND LYMPHADENECTOMY

Kolstad, P., Asmussen, M., Radiumhospitalet, Dept. of Gynaecological Oncology, *Montebello, Oslo 3, Norway*

OBJECTIVE: A prospective study of urinary tract dysfunction after radical surgery for cervical cancer was assessed by utilizing simultaneously urethro-cystometry, radiological video filming, urinary flow measurement and isotope renography and ERPF (effective renal plasma flow).

APPROACH: Twenty-five women, who underwent radical surgery as the only treatment for cancer of the cervix, were examined with simultaneous urethro-cystometry, video filming, flow measurement, isotope renography and ERPF 1) before operation, 2) 2 weeks after operation, 3) one year after operation. All the patients were operated on by the same surgeon using a standardized technique.

Dysfunction such as paralytic bladder, altered bladder sensibility, residual urine, altered micturition pattern, altered urethral resistance, changes in the bladder capacity, changes in urethral and kidney function were all evaluated.

PROGRESS: Using the standard technique of radical hysterectomy and pelvic lymphadenectomy for treatment of cervical cancer at the Norwegian Radium Hospital, we find that the incidence of urinary tract dysfunction is low. The high incidence of long-term dysfunction in the urinary tract as described by several authors cannot be confirmed.

390. THERAPEUTIC RESULTS OF SURGERY IN DYSPLASIAS, MODERATE INTRAEPITHELIAL NEOPLASIA AND CARCINOMA IN SITU OF THE UTERINE CERVIX (ABBREV)

Toledo, P. H., Salas, C. O., Iglesias, J. M., Hospital del Salvador, Unidad de Patologia Cervical, *Casilla 70-D, Calle Carlos Wilson 1341, Santiago 9, Chile*

OBJECTIVE: To evaluate within our setting, the use of cryosurgery in the treatment of dysplasias, moderate intraepithelial neoplasia and carcinoma in situ of the uterine cervix.

METHOD: Cryocauterization of exocervical lesions diagnosed by repeatedly abnormal Papanicolaou tests, exocervical biopsy and scraping the endocervical canal by colposcopy.

Analysis of results by study of cone biopsy will be performed on all patients three months after the cryosurgery in each case in which the histologic alterations derived from the cryosurgery have been eliminated.

391. CRYOSURGERY FOR CERVICAL CANCER

Creasman, W. T., Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina,* 27710, United States of America

This is part of a broader project. A summary of this subproject is not available.

392. TREATMENT OF DYSPLASTIC CERVICAL LESIONS WITH LOCAL CYTOSTATIC (5-FLUORACILO CREAM)

Aruta, C. J., Centro Patologico Cervical, *Casilla 986, Santiago, Chile*

Vaginal dysplasias and some cervical dysplasias are being treated by application of a local cytostatic (5-Fluoracilo cream). We would like to emphasize the importance of colposcopic inspection of the vaginal walls, above all in those cases in which the colposcopist is unable to locate the site of origin of the exfoliated atypical cells (in cases of altered Pap smears) in either the exo- or endocervix. Cases treated to date have been successful, which encourages us to continue this procedure.

393. COMPARISON OF CIS-PLATINUM DOSAGES IN TREATMENT OF ADVANCED CARCINOMA OF THE CERVIX

LaGasse, L. D., University of California, Los Angeles Campus, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California,* 90024, United States of America

This is part of a broader project. A summary of this subproject is not available.

394. CHEMOTHERAPY IN SQUAMOUS CANCER OF UTERINE CERVIX AND VULVA (HUMAN)

Vogl, S. E., Yeshiva University, Bronx Campus, Albert Einstein School of Medicine, Dept. of Medicine, *1300 Morris Park Ave., Bronx, New York,* 10461, United States of America

This is part of a broader project. A summary of this subproject is not available.

395. STUDY OF TRANSFER FACTOR THERAPY IN PATIENTS WITH CERVICAL CANCER

Gitsch, E., Wagner, G., Knapp, W., Tatra, G., Rainer, H., Universitat Wien, Dept. of Obstetrics & Gynecology, *Spitalgasse 23, 1090 Vienna, Austria*

OBJECTIVE: To investigate whether transfer factor therapy can improve the survival rate or delay the appearance of recurrent disease in patients with invasive squamous cell carcinoma of the cervix uteri.

APPROACH: Patients with histologically defined stage Ib or II of a squamous cell carcinoma of the cervix uteri receive about six weeks after radical operation (according to Latzko-Meigs or Wertheim) a radiotherapy by contact irradiation and/ or teletherapy.

Immediately before radiotherapy and then every 4 weeks patients receive in a double-blind manner either placebo or 2E of a transfer factor (TF) preparation (1E is equal to TF from 10 to the 9th power leukocytes). TF is prepared from husbands of patients with cervical carcinoma who are immunologically tested and sensitized against DNCB and KLH before leukocyte donation.

Clinical parameters: delay in recurrence and increase in survival time. Immunological parameters: immune status before and after operation, after radiotherapy and then every three months; testing for transfered sensitivity against DNCB or KLH.

PROGRESS: So far 28 patients have entered the study. No side effects have been seen.

396. NON-SPECIFIC ADJUVANT IMMUNOTHERAPY IN THE RADIATION TREATMENT OF STAGE III CERVICAL SQUAMOUS CARCINOMA (ABBREV)

Shanta, V., Krishnamurthi, S., Girija, P., Nagarajan, B., Cancer Inst., Radiation Oncology Unit, *Madras 600020, Madras, India*

Stage III cervical squamous cell carcinomas constitute 76% of all cervical cancers seen at the Institute. Radiotherapy per se has achieved so far only a 36% five-year disease-free survival in our series. This study was undertaken to evaluate whether a non-specific immunogenic agent like C. parvum would enhance cervical as well as pelvic tumor resolution.

Forty cases were entered into the trial, 20 study subjects and 20 controls. All were Stage III cervical squamous cell carcinomas. All received radiation therapy using a Cobalt-60 beam through 3 portals to deliver a mean tumor dose of 6,000 rads in the para-cervical cube, in about 6 weeks. No intracavitary therapy was used in any of these cases.

C. parvum was administered in the following protocol to the study group: 1) 20 mg I.V. infused in physiological saline one week prior to radiation; 2) 4 mg in physiological saline as I.V. bolus and 4 mg as intraparametrial injection weekly during the course of the radiation therapy; 3) 4 mg of C. parvum as intravenous bolus weekly for 8 weeks after the end of the radiation therapy.

The controls received only physiological saline on the same protocol as C. parvum in the study cases.

The criterion of favorable response was total clinical healing of the pelvic tumor within the volume of irradiation at 8 weeks after the end of the radiation therapy. The evaluation was blind.

A favorable response was obtained in 66.66% of the study cases and 62.5% of the controls. There was no therapeutic advantage in the C. parvum group. Apart from a pyrexial reaction on the day of the C. parvum injection no other toxicity was noticed.

397. COMBINATION THERAPY IN UTERINE CERVIX CANCERS - C. PARVUM PLUS RADIATION

Shanta, V., Krishnamurthi, S., Gopalan, N., Cancer Inst., Dept. of Radiation & Medical Oncology, *Madras 600020, Madras, India*

OBJECTIVE: To evaluate the usefulness of non-specific systemic immunologic stimulation in the treatment of stage III carcinomas of the uterine cervix.

APPROACH: A concurrent randomized controlled clinical trial combining C. parvum with radiation as opposed to radiation alone is under way in stage II-B and stage III squamous cell carcinomas of the uterine cervix.

PROGRESS: To date 18 cases have entered the trial - 9 study and 9 controls. C. parvum is administered I.V. and intraparametrially. The trial is in progress.

398. USE OF CELL KINETICS TO PLAN HUMAN TUMOR TREATMENT

Barranco, S. C., University of Texas, Medical Branch at Galveston, School of Medicine, Dept. of Human Biological Chemistry & Genetics, *300 University Blvd., Galveston, Texas, 77550*, United States of America

The overall objectives of this proposal are to design and test optimal strategies of cancer treatment in humans based on the concepts of the cell cycle and tumor cell population kinetics (Project A). Human tumors such as melanomas, carcinoma of the cervix, and epidermoid carcinoma of the head and neck are accessible for multiple biopsies and for growth kinetics studies such as cell cycle times and growth fractions. Our preliminary studies show that sequential and systematic kinetics analyses of biopsy specimens before, during, and after treatment with a single drug or radiation allow more accurate scheduling of subsequent agents and have led to improvements in response rates. Several intermediate research objectives will be concerned with the development of mathematical models and computational techniques to characterize human tumor growth and to predict and evaluate response to kinetics-based therapy (Project B). By using human tumor kinetics data obtained by FMF analysis in conjunction with appropriate mathematical models and computational techniques (which have been developed and described in Project B), one can readily determine the in vivo kinetics effects of drugs and radiation. Some treatment protocols developed from such modeling studies may depart radically from accepted standard treatment modalities and these will be tested in the 15091A anaplastic carcinoma model in A/J strain white mice (Project C). In addition, this animal model will be used to further characterize and explore the kinetics effects of drugs, radiation and hyperthermia combinations, and fractionations.

Our overall goals, therefore, are to expand our kinetics studies in human tumors; to obtain more accurate data on recruitment and synchrony; and to develop kinetics-based mathematical models which will be used for the design of more effective treatment protocols.

BIBLIOGRAPHIC REFERENCES: Barranco, S.C., Drug Effects on the Cell Cycle, in Effects of Drugs on the Cell Nucleus, eds. Busch, H., Crooke, S., and Daskal, Y. Academic Press, 455-473, Vol. 1, 1979. Barranco, S.C., Cell Cycle: Drug Effects and Clinical Application in Cancer and Chemotherapy, eds. Crooke, S. Academic Press, 123-135, Vol. 1, 1980.

399. STUDIES OF PATIENTS WITH DISSEMINATED SOLID TUMORS

Krakoff, I. H., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

Independently and not as an agent of the Government, the Contractor shall exert its best efforts to conduct Phase II and Phase III studies in patients with disseminated solid tumors. The tumors to be included in these studies shall be limited to the following: lung carcinoma; ovarian carcinoma; cervical carcinoma; head and neck carcinoma; prostatic carcinoma; bladder carcinoma; and melanomas and sarcomas of soft tissue. A minimum of 400 patients shall be included in these studies with no fewer than 25 patients from any one tumor type. All patients shall be treated intensively with chemotherapy either alone or in combination with other drugs, radiotherapy, immunotherapy or surgery in protocols to be agreed upon by the Project Officer and Principal Investigator. Protocols will include Phase II testing of new investigational drugs, Phase II testing of standard antitumor drugs not previously tested against the particular tumor type, as well as Phase III trials to determine the definitive activity of the above regimens.

B. THERAPY OF OVARIAN CARCINOMA

400. COMBINATION CHEMOTHERAPY IN TREATMENT OF OVARIAN CANCER (ABBREV)

Razis, D. V., Dimitriades, M., Poulakou, E., Petounis, A., Diagnostic & Therapeutic Inst. of Piraeus, Dept. of Medicine, *51 Botassi St., Piraeus*, 30, Greece

OBJECTIVE: To study the effectivenss and toxicity of the therapeutic scheme cis-platinum, adriamycin, cyclophosphamide and hexamethyl-melamine and compare this scheme with the 5-FU, cyclophosphamide, actinomycin-D and corticosteroids combination ('modified Cooper') in ovarian cancer.

APPROACH: Cancer of the ovary stages III-IV (FIGO) proven with histological diagnosis (usually taken during the exploratory laparotomy) are randomized to CPDD combination and to 'modified Cooper' scheme. Patients in the CPDD combination are treated as follows: Day 1: Adriamycin 302mg/m2 I.V. push, cyclophosphamide 300 mg/m2 I.V. push, cis-platinum 50 mg/m2 in 6-8 hours I.V. infusion. Days 3-16: Hexamethylmelamine 6 mg/kg daily p.o. The CPDD is administered after prehydration while mannitol diuresis is induced during th CPDD infusion in order to keep the diuresis to more than 100 cc/hr. The cycle is repeated every month. If complete remission is obtained, we treat the patient with at least 12 cycles. Patients randomized to 'Cooper's' regimen are treated as follows: 5-FU 500 mg I.V. push daily, Days 1-5, cyclophosphamide 300mg. I.V. push Days 1 and 4, vincristine 1-1.5 mg, I.V. push Days 1 and 4, actinomycin-D 1 mg I.V. push, Days 2 and 5, and prednisone 50-75 mg I.M. Days 1-5. The cycle is repeated monthly. If complete remission is obtained we treat the patient for 3 years. In case of failure with either scheme we cross over to the other regimen and if complete remission is achieved we treat the patient as described above. If however, we achieve only partial remission we alternate monthly Cooper's scheme with CPDD combination.

PROGRESS: The CPDD combination has been under study in the Department of Medicine of the Cancer Institute of Piraeus for 14 months and will probably terminate on December 31, 1979. Objective responses to CPDD combination are now up to 77% (15% CR) lasting for at least 3 months. The modified Cooper's regimen has been under study in our Institute for years. The objective responses are 50-60% with 15-20% CR.

401. SUPPORT OF CLINICAL TRIALS IN THE DIVISION OF ONCOLOGY AT SUNNYBROOK MEDICAL CENTRE

Osoba, D., Sunnybrook Hospital Medical Centre, Division of Oncology, *2075 Bayview Ave., Toronto, Ontario*, M4N 3M5, Canada

Patients with histologically proven cancer are being entered into a variety of clinical trials. These include: 1. Chemotherapy of small carcinoma of the lung with cyclophosphamide, adriamycin and vincristine, including prophylactic brain irradiation. 2. Chemotherapy of disseminated non-small cell carcinoma of the lung with cyclophosphamide, adriamycin and cis-platinum or 5-fluorouracil, adriamycin and mitomycin-C. 3. Immunotherapy of resectable stage I or II non-small cell carcinoma with Freund's adjuvant and tumor cell wall antigen. 4. Immunotherapy of stage I or III resected malignant melanoma with either BCG or levamisole or BCG and levamisole. 5. Chemotherapy of advanced renal adenocarcinoma with vincristine and hydroxyurea. 6. Chemotherapy of stage III or IV epithelial carcinoma of the ovary with either melphalan or hexamethylmelamine, cyclophosphamide, adriamycin and 5-fluorouracil or cyclophosphamide, adriamycin and cis-platinum. 7. A phase I trial of the capacity of oral folinic acid to prevent toxicity of oral methotrexate. 8. Combined trial of chemotherapy with CCNU and hydroxyurea and irradiation in grade III or IV astrocytoma. Approximately 50-70 patients/year are entered in the above trials.

402. THERAPEUTIC TRIALS IN PATIENTS WITH ADVANCED OVARIAN CANCER

Tuskan, E., Pavic, A., Muzaferija, A., Lovric, B., Medical Center, Dept. of Gynecology & Obstetrics, *Karlovac, Yugoslavia*

The problems of prevention and early detection of ovarian cancer are still unsolved. Due to the asymptomatic course of that disease, it is often diagnosed late so that the results of treatment are inadequate. In advanced ovarian cancer, palliative surgical procedures, chemotherapy, and selective radiotherapy often have to be applied.

Cytostatics, either alone or in combination, suppress the growth of cancer cells. Regression in the number of cancer cells due to necrosis results in endotoxic effects and various components of decomposed tumor are responsible for cachexy and immunity suppression.

To prevent the endotoxic effect it is necessary to remove residual tumor after chemotherapy. The aim of our study was to determine the favorable term for the 'second look' operation. Primary tumor volume was reduced to 50 percent approximately after 5 courses of chemotherapy. Only one course of chemotherapy is enough to destroy about 90 percent of the cancer cells, as the 7-day course covers at least 2 cell cycles. In that phase of disease the cancer is subclinical, local findings show the evident regression of tumor volume, and the patients feel better.

We propose indicating the cyto-reductive surgery just in that phase of disease with removal of the necrotic cancer tissue and if possible with reduction of residual tumor. After the 'second look' operation it is necessary to repeat the whole process at least two times more. In that case changing the protocol is favorable so that refractoriness could be prevented.

403. CLINICAL TRIALS AND MISCELLANEOUS CLINICAL INVESTIGATIONS

Young, R. C., Chabner, B. A., Fisher, R. I., Lippman, M., Myers, C., Whang Peng, J., DeVita, V. T., Simon, R., Rosenberg, S., Longo, D., Ozols, R., Glatstein, E., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Medicine Branch, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The Medicine Branch is a major clinical facility of the National Cancer Institute. Its activities are divided between clinical therapeutic trials in patients with cancer and clinically related laboratory research. Clinical trials of cancer treatment in the following diseases are currently underway: breast cancer, ovarian cancer, Hodgkin's disease, non-Hodgkin's lymphomas, testicular tumors, melanoma, cervical carcinoma, and endometrial carcinoma. In addition, Phase I-II clinical trials have been completed this year on the following new experimental agents or combinations: AMSA, PALA and 5-Fu, chlorozotocin, ICRF-187, and pentamethylmelamine. Phase I-II trials continue on AZQ, 13-cis-retinoic acid, intraperitoneal chemotherapy of 5-FU and adriamycin. Additional summaries of clinical studies appear under reports entitled 'Clinical Program in Breast Carcinoma.' Laboratory research of the branch is summarized under reports entitled 'Clinical Pharmacology of Antineoplastic Agents, Kinetics of Cellular Proliferation.'

BIBLIOGRAPHIC REFERENCES: Ozols, R.F., Garvin, A.J., Costa, J., Simon, R.M., Young, R.C.: Advanced ovarian cancer: correlation of histologic grade with response to therapy. Cancer 45: 572-581, 1980. Young, R.C.: Chemotherapy of the gynecologic malignancies. In Cancer Chemotherapy 1980. H.M. Pinedo (Ed). Amsterdam: Exerpta Medica, 1980. In press.

404. COMBINATION CHEMOTHERAPY IN ADVANCED OVARIAN CANCER (HUMAN)

Greenwald, E. S., Montefiore Hospital & Medical Center, *111 E. 210th St., Bronx, New York*, 10467, United States of America

This is part of a broader project. A summary of this subproject is not available.

405. CHEMOTHERAPY AND CHEMOIMMUNOTHERAPY OF CANCER

Holland, J. F., Bekesi, J. G., Bruckner, H., Bhardwaj, S., Cuttner, J., Chahinian, A. P., Slankard Chahinian, M. L., Fernbach, B., Goldsmith, M., Hart, R., Himori, T., Keusch, G., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

In the last calendar year, Program Project Grant (CA15936-05) has been vigorously pursued by the investigators of the Mount Sinai School of Medicine under the Principal Investigatorship of James F. Holland, M.D.

Chemoimmunotherapy of acute myelocytic leukemia continues to provide exciting data.

Research in lung cancer has involved the investigation of a 4-drug combination regimen, MACC plus levamisole, and MACC plus C. parvum.

Our investigation of 4-drug second line chemotherapeutic responses in disseminated breast cancer continues to be productive.

Adriamycin and platinum continue to be the central building blocks for chemotherapeutic regimens in patients with ovarian cancer.

A continuing assessment of our chemotherapeutic regimens in prostatic cancer identifies 15 of 19 responders with six of eight with measurable lesions showing 6% or more regression of the disease. Remaining responders all were characterized by major reduction in pain and reduction in alkaline and acid phosphatase.

Gastrointestinal cancer investigations continue with a central attention to fluorouracil by continuous infusion and intermittent intravenous bolus dosing with mitomycin-C and oral treatment with hexylmethylmelanamine.

Experimental chemotherapy has included active clinical investigation of several new drugs, m-AMSA, maytansine, dichloromethotrexate, L-phosphonoacetyl-l-aspartate (PALA), indocine-n-oxide, and L-alanosine.

In the microbiological research, serum opsonins as the determinant of success in granulocyte transfusions continue under study.

Analytical biochemistry of opportunistic infections has made major progress in identification of D-arabinitol, a metabolite of Candida albicans which can be reproducibly quantified in human serum.

BIBLIOGRAPHIC REFERENCES: Takahashi, I., Ohnuma, T. and Holland, J.F.: Comparison of biological effects of dichloromethotrexate and methotrexate on human leukemia cells in culture. Cancer Res. 39:1264-1268, 1979. Ambinder, E.P., Perloff, M., Ohnuma, T., Biller, H.F. and Holland, J.F.: High dose methotrexate followed by citrovorum factor reversal in patients with advanced cancer. Cancer 43:1177-1182, 1979.

406. PHASE II STUDY OF ANGUIDINE IN SOLID TUMORS

Niell, H. B., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

Anguidine is a Phase II investigational drug that is being evaluated for the use in patients with solid tumors who have been shown to be refractory to standard therapy. This investigational drug has been shown in the mouse model to be effective against the P388 leukemia model and the murine colon tumor. The side effects have not been excessive in animal and in man, however, every effort will be made to monitor closely any side effects that may occur. It will be tried against the following tumors: Hodgkin's disease refractory to treatment, non-Hodgkin's lymphoma, breast cancer, oat-cell carcinoma of the lung, adenocarcinoma, large cell and epidermal carcinoma of the lung, GI cancers such as cancers of the stomach and the pancreas, sarcomas, ovarian carcinoma, endometrial carcinoma, renal cell carcinoma and testicular carcinoma. It is hoped that by studying this agent we will demonstrate an effectiveness in one of these human tumors and therefore add a good anti-cancer drug to our present chemotherapeutic regimen.

407. PHASE II STUDY OF MAYTANSINE IN SOLID TUMORS

Niell, H. B., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

This is a Phase II study of the investigational drug, Maytansine, against human solid tumors that have been previously refractory to standard therapy. This drug has demonstrated good activity against the mouse P388, a lymphocytic leukemia model. The side effects are not excessive, at least in early human and animal models. Several human tumors, including oat cell carcinoma of the lung, malignant melanoma, and cancers of the breast and head/neck demonstrated in Phase I studies some response rates. We will test this drug in patients who have been refractory to Hodgkin's disease, non-Hodgkin's lymphoma, breast, small cell of the lung and non-oat cell carcinoma of the lung, GI tract carcinoma, sarcomas, ovarian carcinoma, endometrial carcinoma, renal carcinoma and testicular carcinoma. It is hoped that by testing this drug we will add a new drug to our chemotherapeutic regimen for this group of diseases in which therapy is inadequate.

408. A PHASE II TRIAL ON NEOCARZINOSTATIN

Spaulding, M. B., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

Neocarzinostatin is an investigational drug to be used in patients with histologically confirmed carcinoma of the bladder, kidney, pancreas, stomach, uterus, and ovary, hepatoma, acute leukemia, or malignant melanoma after the usual first line treatments have been exhausted. The objectives of this study were to determine response frequency, response duration, and survival duration in patients treated and to determine the frequency and severity of organ system toxicities associated with Neocarzinostatin. This is part of a larger study and the results are not available at this time.

409. CIS-DIAMMINEDICHLOROPLATINUM II FOR OVARIAN CANCER (HUMAN)

LaGasse, L. D., University of California, Los Angeles Campus, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

This is part of a broader project. A summary of this subproject is not available.

410. CHEMOTHERAPY OF ADVANCED MALIGNANCIES - SWOG 7524

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

Chemotherapy of Advanced Malignancies - The objectives of the protocols herein contained are to improve the results of treatment for patients with non-Hodgkin's lymphomas and squamous carcinoma of the head and neck. In the former situation a prospective, randomized comparison of two different combination chemotherapy regimens and one chemoimmunotherapy program is to be carried out. In the latter, patients are to be randomized between methotrexate alone, a standard form of treatment, and a three-drug combination combining Methotrexate and 2 other active drugs. Comparisons will be made based on response rate, toxicity and survival data. As soon as a conclusion can be reached regarding superiority of a particular regimen, these studies will be closed.

SWOG 7524 - To compare the effectiveness of chemotherapy alone (adriamycin-cyclophosphamide) vs. chemoimmunotherapy (adriamycin-cyclophosphamide plus BCG) for remission induction in patients with Stage III and IV ovarian and endometrial carcinoma who have had no previous cytotoxic chemotherapy. To test the effectiveness of continued chemoimmunotherapy vs. chemotherapy in maintaining complete remissions (documented) achieved during the initial 12 month induction therapy. To test the effectiveness of continued chemoimmunotherapy vs. chemotherapy in inducing complete remissions or maintaining partial remissions in patients with occult disease at the time of restaging for complete response or in patients achieving only partial clinical remission during the initial 12 month induction therapy. This study was activated in October of 1974 and closed in October of 1976. All patients from this center were entered into the study. 154 were entered groupwide. The data showed that adriamycin-cyclophosphamide plus BCG was better than adriamycin-cyclophosphamide alone in terms of actuarial survival. No further case entries are anticipated.

411. PHASE II STUDY OF ARABINOSYLADENINE-5'-PHOSPHATE (ARA-A-5'-P)

LePage, G. A., Khaliq, A., University of Alberta, Cancer Research Unit, McEachern Laboratory, *Edmonton, Alberta, Canada*

OBJECTIVE: To determine the efficacy of Ara-A-5'-P in the treatment of selected clinical cancers.

APPROACH: Samples of the malignant cells (biopsy, bone marrow, peripheral blasts of leukemias, as suitable) are incubated in a cell culture medium with tritiated thymidine and various levels of Ara-A. Measurements are made of the sensitivity of DNA synthesis in these cells, as measured by the incorporation of tritiated thymidine, to various levels of Ara-A. Patients so selected are treated once daily for 10 days by i.v. injection of Ara-A-5'-P at 1300 mg/m2. A course is given every 28 days.

PROGRESS: Of some 25 patients treated, 1 chronic myelogenous leukemia in blastic crisis, 1 non-Hodgkin's lymphoma, 1 ovarian carcinoma, 1 melanoma and 2 myelomas have shown objective responses. A correlation has been observed between sensitivity in the above test and clinical response.

412. THE CHEMOTHERAPY OF METASTATIC GENITOURINARY TUMORS

Ostrow, S., Wiernik, P. H., Aisner, J., Konits, P., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Medical Onclogy Section, *Baltimore, Maryland*, 21201, United States of America

Cis-platinum and adrimycin have been shown to have activity against testicular carcinoma. This drug combination was used for genitourinary neoplasms. Thirty-nine patients received therapy with platinum and adriamycin. Complete responses occurred in five of 11 patients. Partial responses occurred in four patients with testicular carcinoma. The median duration of response will exceed eight months. Partial responses have been seen in one patient with Wilms' tumor, 5/9 patients with bladder cancer, 4/9 patients with ovarian cancer and 1/4 patients with prostate cancer. Two patients are too early to evaluate, and three patients were evaluable only for toxicity. Dose reduction and delay in therapy was necessary because of bone marrow suppression. Nephrotoxicity occurred in 7 patients and necessitated discontinuing platinum one. Other toxicities included ototoxicity and neurotoxicity. The combination of platinum and adriamycin is active against advanced genitourinary neoplasms and further studies are comtemplated to enhance therapeutic efficacy. Other combinations will be used for testicular cancer.

413. TREATMENT OF OVARIAN CANCER WITH COMBINATION CHEMOTHERAPY AND BONE MARROW INFUSION

Herzig, G. P., Washington University, School of Medicine, Dept. of Internal Medicine, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

This is part of a broader project. A summary of this subproject is not available.

414. AN EVALUATION OF THE ROLE OF ALLOGENEIC AND AUTOLOGOUS MARROW TRANSPLANTATION IN THE MANAGEMENT OF MALIGNANT DISEASES

Biggs, J. C., Ma, D., Pun, A., Johnson, L., Bashir, H., Penny, R., Vincent, P., St. Vincent's Hospital, Dept. of Haematology, *Victoria St., Darlinghurst, N.S.W. 2010, Australia*

OBJECTIVE: In this project, the role of allogeneic transplantation in the management of leukemia and lymphoma will be evaluated; furthermore, the role of autologous marrow transplantation will be evaluated in the management of acute leukemia, chronic granulocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma and certain solid tumors e.g., sarcomas, ovarian carcinoma and testicular tumors.

APPROACH: (a) An evaluation of cryopreservation methods is being undertaken. (b) Techniques for the measurement of viability following thawing of marrow cells are being established. (c) Allogeneic transplants following total body irradiation are being studied in acute adult leukemia during the first relapse. (d) Patients' remission marrow in acute leukemia and marrow in chronic granulocytic leukemia are being stored and used after thawing for autologous transplantation during subsequent therapy of acute relapses. (e) Cryopreservation of marrow in patients with sensitive solid tumors is being undertaken for subsequent autologous transplantation during chemoradiotherapy for relapse.

415. SPECIFIC IMMUNOTHERAPY WITH MONOCLONAL ANTIBODIES

Bast, R. C., Ritz, J., Knapp, R. C., Sidney Farber Cancer Institute, *44 Binney St., Boston, Massachusetts*, 02115, United States of America

Using somatic cell hybridization techniques, monoclonal antibodies have been prepared against two human malignancies, acute lymphoblastic leukemia (ALL) and ovarian carcinoma. Studies are proposed to examine the pharmacokinetics and toxicity of these reagents after intravenous or intraperitoneal infusion. Methods will be sought to utilize or to prevent antibody-induced modulation of antigens from the surface of ALL cells. Monoclonal antibodies will be used to eliminate leukemic cells from bone marrow before antigenic modulation occurs, facilitating effective autologous marrow transplantation. Attempts will be made to analyze the capacity of antibodies of different subclasses to activate cellular or humoral effector mechanisms. The immunostimulant C. parvum will be administered to augment cellular effector function for antibody dependent tumor cell lysis. These studies should help to provide a more rational basis for the use of monoclonal antibodies for serotherapy of human cancer.

416. AUTOLOGOUS MARROW TRANSPLANTATION

Buckner, D., Thomas, E. D., Stewart, P., Bensinger, W., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

We propose to evaluate the effectiveness of high dose chemoradiotherapy in a variety of malignant diseases including acute leukemia, chronic granulocytic leukemia, oat cell carcinoma, malignant lymphoma, ovarian carcinoma, breast carcinoma and resistant pediatric solid tumors. Patients will have marrow cryopreserved prior to therapy and reinfused following intensive therapy with regimens developed in the syngeneic and allogeneic transplant programs. The effectiveness of this approach in terms of marrow repopulation and therapeutic effectiveness will be evaluated.

417. IMMUNOTHERAPY IN OVARIAN CARCINOMA

Juillard, G. J., University of California, Los Angeles Campus, School of Medicine, Dept. of Microbiology & Immunology, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

This is part of a broader project. A summary of this subproject is not available.

418. IMMUNOTHERAPY OF OVARIAN CARCINOMA

Knapp, R. C., Harvard University, Boston Campus, School of Medicine, Dept. of Radiation Therapy, *25 Shattuck St., Boston, Massachusetts*, 02115, United States of America

This is part of a broader project. A summary of this subproject is not available.

419. SURVEY OF GENERAL HOSPITAL PRACTICE WITH REGARD TO CANCER OF SELECTED SITES

Tognoni, G., Franzosi, M. G., Mancini, M., Liberati, A., Mantovani, A., D'Incalci, M., Istituto di Ricerche Farmacologiche Mario Negri, Dept. of Clinical Pharmacology, *Via Eritrea 62, 20157 Milan, Italy*

OBJECTIVE: Survey of general hospital practice in the diagnosis, treatment, and follow-up of patients with breast cancer, lung cancer, cancer of the ovary, and Hodgkin's and non-Hodgkin's lymphomas.

APPROACH: Retrieval and analysis (auditing) of medical records of all admitted cases with the above mentioned diagnoses during 1978, and first diagnoses of the same cancer types for 1979.

PROGRESS: Recruitment of hospitals has been completed to include 36 hospitals from 5 Italian regions. Retrieval of cases will be completed by March 1980.

420. OVARIAN CARCINOMA INTENSIVE THERAPY

Thomas, E. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

421. THERAPY OF PATIENTS WITH OVARIAN CARCINOMA

Decker, D. G., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

422. IN VITRO STUDIES OF OVARIAN CANCER - EFFECT OF CYTOSTATIC AGENTS, STEROID HORMONES, BLOCKING SERUM FACTOR AND MRF (ABBREV)

Carstensen, H. C., University Hospital, Dept. of Gynecology, *S58185 Linkoping, Sweden*

Clones of malignant tumor cells are derived from patients with ovarian cancer and cultured in vitro. The effects of cytostatic agents, steroid hormones, patient's own lymphocytes with and without patient's own serum and Muellerian regression factor (MRF) on cell kinetics, on DNA and RNA synthesis, on protein synthesis (when applicable) as well as on the presence and number of estrogen and progestogen receptors will be studied.

423. PLASMA PHARMACOKINETICS AND IN VITRO RESPONSE OF OVARIAN CANCER CELLS TO CHEMOTHERAPEUTIC AGENTS

Morasca, L., D'Incalci, M., Sessa, C., Erba, E., Istituto di Ricerche Farmacologiche Mario Negri, Dept. of Cancer Pharmacology, *Via Eritrea 62, 20157 Milan, Italy*

OBJECTIVE: The main objective of the project is to compare in plasma the availability of active anticancer drugs or metabolites measurable after the administration of a therapeutic dose with the concentrations and lengths of exposure of cancer cells from the same patient needed to produce a measurable impairment of their viability.

APPROACH: The plan is developed along two lines: improvement of methods for measuring plasma levels of the active compounds resulting from administration of anticancer agents known to be active on ovarian cancer and setting-up of a reliable tissue culture method which would allow to maintain ovarian cancer cells in good condition long enough to permit their exposure to drugs for periods of time comparable to those encountered in vivo.

PROGRESS: At this stage methods for measuring adriamycin and hexamethylmelamine with some metabolites are already satisfactory while work is still in progress to obtain good measures of melphalan.

The tissue culture method developed for ovarian cancer cells gave satisfactory preparations and quantitative evaluations of cell survival impairment. The study is in progress.

424. CORRELATIONS BETWEEN PHARMACOKINETICS AND ACTIVITY OF ANTINEOPLASTIC AGENTS

Donelli, M. G., Ghersa, P., Colombo, T., Broggini, M., Istituto di Ricerche Farmacologiche Mario Negri, Dept. of Cancer Chemotherapy in Vivo, *Via Eritrea 62, 20157 Milan, Italy*

OBJECTIVES: Study the distribution of adriamycin (AM), bis-chloroethylnitrosourea (BCNU) and hexamethylmelamine (HMM) in experimental tumor models of the rat and the mouse treated with different doses and schedules. Investigate whether correlations exist between drug levels in vivo and cytotoxic effects. Investigate the influence of physiological, pathological and pharmacological factors on the distribution of these drugs and the metabolic pharmacokinetic interaction in the combined use of drugs.

APPROACH: The distribution of AM, BCNU and HMM is investigated in CD rats bearing Walker 256 carcinosarcoma and in C57Bl/6 mice bearing Lewis lung carcinoma after a single high-dose treatment and repeated low-dose treatments at different intervals. Drug levels achieved at the various sites under different treatment conditions are correlated with the therapeutic or toxic effects elicited and when possible, concentration-response curves are constructed. Animals of different ages, sexes, strains or submitted to various preceding treatments with different drugs are also utilized to study the influence of the above mentioned factors on the distribution of these compounds.

The adriamycin-methotrexate pharmacokinetic interaction is studied in C3H mice bearing a mammary carcinoma and the antitumoral effect of this interaction is investigated.

PROGRESS: Study of plasma and tissue pharmacokinetics of HMM and its demethylated metabolites, pentamethylmelamine and tetramethylmelamine, given by different administration routes to mice bearing the ovarian tumor M5076/73A is in progress.

425. IMMUNOTHERAPY OF MOUSE OVARIAN CANCER

Bast, R. C., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts*, 02115, United States of America

OBJECTIVE: Attempt to evaluate the therapeutic efficacy of specific xenogeneic serotherapy in combination with intraperitoneal C. parvum in the treatment of syngeneic murine ovarian carcinoma transplants. Efforts will be made to determine the optimal dose, route, order, and schedule of administration for this combination. Attempts will be made to determine relevant in vitro correlates with disease status. Techniques will be perfected for the cryopreservation of human ovarian tumor cells and for the preparation of specific xenoantiserum against human tumor cells. Ultimately, information gained in the mouse model system will be applied to the development of human clinical trials to be conducted only under specific clinical protocols approved by the Project Officer. No such human clinical studies will be conducted in the first year. Any modification of the study design must have the written approval of the Project Officer before being instituted.

426. RESPONSE TO THERAPY OF HUMAN OVARIAN CANCERS IN VIVO AND TRANSPLANTED IN MICE (ABBREV)

Davy, M. L., Radiumhospitalet, Dept. of Gynaecology, *Montebello, Oslo 3, Norway*

OBJECTIVE: To compare the response to therapy of human tumors in the patient with that of the implanted tumor in nude mice.

APPROACH: Patients operated on for gynecological tumors who had not received previous therapy were selected. Small pieces of viable tissue from the tumor were xenografted subcutaneously onto the backs of nu/nu mice. Studies of light and electron microscopy and isoenzymes are done to determine that the tissue preserves its human characteristics. Patients are treated according to a protocol, and if the tumor 'takes' in the mouse, serial transfer is done and this same therapy, irradiation or chemotherapy is given to the mice. Comparisons are then made of the response in the two systems.

As an extension of the practical uses of the system, other drugs are tested against these tumors in an effort to build up the group of drugs likely to be active against a given histological type.

PROGRESS: Fifteen gynecological tumors are now established in nude mice - ovarian cancer, cervical cancer and sarcomata. Irradiation techniques are tested and both single agents and multiple drugs are currently being tested, as well as some preliminary experiments with radiosensitising agents metronidazole and misonidazole. A clinical trial treating sarcomas with adjuvant chemotherapy is also under way.

C. THERAPY OF UTERINE CANCER

427. TREATMENT OF ADVANCED ENDOMETRIAL CANCER WITH PROGESTOGENS

Masi, C. A., Ellena, A. N., Bertoli, R., Inst. Nacional Regional de Oncologia, Dept. de Ginecologia, *Bv. Zavalla 3399, C.C. No. 366, 3000 Santa Fe, Argentina*

OBJECTIVE: To determine the effects of the activities of various progestogens on the clinical response of patients receiving palliative treatment for advanced endometrial cancer.

METHODS: Response to treatment will be evaluated by the following parameters: a) persistence, b) progression, c) regression. The subjective reaction will also be considered.

428. DIAGNOSIS, TREATMENT AND FOLLOW-UP OF PROLACTINOMA ACTIVITY OF PITUITARY GONADOTROPHS AND LACTOTROPHS IN PATIENTS WITH ENDOMETRIAL CARCINOMA

Crosignani, P. G., Universita degli Studi di Milano, Clinica Ostetrica e Ginecologica IV, *12 via Commenda, 20122 Milan, Italy*

OBJECTIVES: 1) Pre-radiological diagnosis of pituitary prolactinoma. 2) Treatment and follow-up of patients with pituitary prolactin secreting adenoma. 3) Evaluation of the activity of pituitary gonadotrophs and lactotrophs during treatment with Depo-Provera in patients affected by endometrial carcinoma.

APPROACH AND PROGRESS: 1) Two new diagnostic tests have been evaluated for the pre-radiological diagnosis of pituitary microadenoma: nomifensine and L-dopa/carbidopa test. The data obtained in a consistent group of hyperprolactinemic patients showed that both tests are unable to discriminate in a single patient between tumorous and nontumorous forms of hyperprolactinemia. The data on the nomifensine test have been accepted for publication in J. Clin. Endocrinol. The data on the L-dopa/carbidopa test have been submitted for publication in J. of Clin. Invest. 2) More than 70 hyperprolactinemic patients are actually studied by our group. A consistent subgroup of these patients (24) is currently treated with metergoline or bromocriptine in order to evaluate the anti-adenoma growth activity of the above mentioned drugs. Each patient undergoes a biochemical (prolactin and progesterone) and a radiological control (tomography or computerized tomography). 3) LRH and TRH tests are performed in patients with endometrial carcinoma before and during treatment with massive (500 mg/week p.o.) doses of Depo-Provera. The data obtained so far are quite limited.

429. SAFER CANCER CHEMOTHERAPY - THE DESIGN OF MULTIPLE DRUG PROTOCOLS (ABBREV)

Hill, B. T., Price, L. A., Imperial Cancer Research Fund, Cellular Chemotherapy Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

The use of antitumor drugs has traditionally been reserved for patients who fail to respond or whose tumors have recurred after standard treatment with radiotherapy and surgery. This understandable reluctance to use chemotherapy, except as a last resort, derives from the mistaken belief that drug therapy is automatically associated with severe toxicity. We have shown that, provided certain precautions are observed, it is possible to administer intensive combination chemotherapy protocols, designed according to certain kinetic principles (see ICRF Scientific Report 1976 - report 59), with safety and without loss of therapeutic benefit. This approach, involving treatment over 24-36 hours rather than several days, has been used effectively against certain advanced malignancies. For example, head and neck cancers (ICRF Scientific Report 1978 - report 18), breast carcinomas (Goldie and Price, British Medical Journal, 1977, 2, 1064) and non-squamous cell lung cancers (Anderson et al. British Journal of Diseases of the Chest, 1977, 71, 179). Ongoing studies include the treatment of advanced endometrial carcinomas (ICRF Scientific Report 1978 - report 20) where 2/6 responses have been noted and pancreatic tumors (in collaboration with Dr. J. Angers, New York, USA) involving treatment with vincristine, mitomycin C, procarbazine, chlorambucil, 5-fluorouracil and pyrimethamine.

Recently we have designed trials based on these principles, for cervical cancer in collaboration with Johannesburg, and for prostatic cancer for the Multicentre U.K. trial. These protocols are all well tolerated by the patients and allow a good quality of life. This safe and effective method of administering combination chemotherapy can now be used to complement local therapy.

430. METABOLIC PATTERNS AND CHEMOTHERAPY OF NEOPLASIA

Weber, G., Ban, J., Aoki, T., Suttle, D. P., Indiana University - Purdue University at Indianapolis, School of Medicine, Dept. of Pharmacology, *1219 W. Michigan St., Indianapolis, Indiana,* 46202, United States of America

BACKGROUND: With present-day treatment, radiation and surgery are capable of curing approximately 50 percent of cancer patients; consequently, effective chemotherapy applicable to most or all cases of neoplastic diseases is urgently needed. Chemotherapy has already shown encouraging progress in the treatment of choriocarcinoma, Burkitt's lymphoma, certain other types of lymphomas and juvenile leukemias, Hodgkin's disease and certain endocrine tumors. However, in the great majority of solid tumors, adult onset leukemias, and especially brain tumors, chemotherapeutic efforts so far have failed to produce lasting results and there is a great deal to be achieved in the rational design of chemotherapy for cancer and allied diseases.

AIM OF THE RESEARCH PROGRAM: (1) The objective of this investigation is to elucidate strategic exploitable metabolic, enzymatic and isozymic differences between normal and neoplastic tissues of different growth rates and differentiation to provide a molecular basis for rationally planned selective enzyme pattern-directed experimental chemotherapy. (2) A thorough understanding of the main differences between normal and cancerous tissues at the molecular level should permit the evaluation of the regulatory mechanisms of gene expression which play crucial roles in the differentiation, replication and functioning of normal and neoplastic cells. It is expected that elucidation of the enzymatic basis of the key metabolic and regulatory alterations in cancerous tissues and an understanding of the factors which govern the pattern of gene expression might permit the design of new drugs and approaches to control neoplastic diseases by chemotherapy. (3) The ultimate goal of this program is to identify key metabolic, enzymatic and isozymic targets for chemotherapy and to develop chemical compounds possessing a high degree of selective toxicity to cancer cells in order to achieve lasting chemotherapeutic results.

431. USE OF TAMOXIFEN IN ADENOCARCINOMA OF ENDOMETRIUM (HUMAN)

Petty, W. M., University of Oregon Health Sciences Center, School of Medicine, Dept. of Surgery, *3181 S.W. Sam Jackson Park Rd., Portland, Oregon,* 97201, United States of America

This is part of a broader project. A summary of this subproject is not available.

432. THE CATHETRON IN THE TREATMENT OF CANCER OF THE UTERUS

Taina, E. J., Vanhatalo, J. H., University Central Hospital of Turku, Depts. of Obstetrics & Gynaecology/Radiotherapy, *SF20520 Turku 52, Finland*

OBJECTIVE: Radium has been used for decades in the treatment of cancer of the uterus. There are, however, certain difficulties in the dosimetry of the treatment and in protecting the staff from the radiation. These difficulties are greatly reduced by using the Cathetron afterloading device in the treatment. Cathetron treatment is new and its effect has not been throughly analyzed yet.

APPROACH: This study will compare radium and Cathetron treatments with each other. The material for the study derives from the patients treated with either radium or the Cathetron in 1969-76. The study is divided into two parts: a clinical and a clinical-biophysical one.

PROGRESS: The material will be analyzed to determine the patients' survival, complications and operability after the treatment. The study also is planned to solve the problems of treatment planning consisting of fractionation, dosage and treatment time. Comparison between TDF and CRE will also be made. The first international afterloading therapy meeting was held in London in 1978 and I was pleased to participate. The results of the present study will hopefully be available at the second meeting planned for 1980.

433. RADIOTHERAPY OF CANCER OF THE BLADDER, BRONCHUS, AND CERVICAL UTERI IN COMBINATION WITH RADIOSENSITIZING DRUGS

Rimondi, C., Busutti, L., Corrado, F., Fasano, E., Pazzaglia, G., Stecchi, V., M. Malpighi Hospital, Dept. of Radiotherapy, *Via Albertoni N. 15, 40138 Bologna, Italy*

The summary for this project is under entry no. 384.

434. RADIATION RESPONSE AND UTERINE CANCER (HUMAN)

Rubin, P., University of Rochester, School of Medicine & Dentistry, Depts. of Medicine/Radiology/Surgery, *601 Elmwood Ave., Rochester, New York,* 14627, United States of America

This is part of a broader project. A summary of this subproject is not available.

435. RADIATION IN UTERINE SARCOMA MANAGEMENT (HUMAN)

Rubin, P., University of Rochester, School of Medicine & Dentistry, Depts. of Medicine/Radiology/Surgery, *601 Elmwood Ave., Rochester, New York,* 14627, United States of America

This is part of a broader project. A summary of this subproject is not available.

436. STAGE I FIGO ENDOMETRIAL CARCINOMA - RADIO-SURGICAL TREATMENT AND PROGESTIN THERAPY IN RELATION TO RISK FACTORS (ABBREV)

Mangioni, C., Periti, P., Universita degli Studi di Milano, Clinica Ostetrica e Ginecologica IV, *12 via Commenda, 20122 Milan, Italy*

Objectives of the present Clinical Study of Stage I (FIGO) endometrial cancer are as follows: 1) Accurate evaluation of neoplastic extension by anatomo-radio-surgical staging; 2) thorough investigation of tumor and host risk factors; 3) objective assessment of the value of post-operative external irradiation in high-risk cases; 4) collection of a large number of cases stratified according to prognostic factors and allocated at random to progestin treatment so that effectiveness of adjuvant medroxyprogesterone acetate can be statistically assessed, at least for the entire population studied; 5) assessment of progesterone and estrogen receptors in a pilot series, with possible correlations with grade, histotype and clinical response, as well as with MAP plasmatic levels.

The Protocol of the Study has been discussed by both principal and affiliated units in a series of meetings held in Milan, Brescia, Florence and Rome in order to collect, define, and unify all emerging instances of cooperation and to select the 19 cooperating Units as follows: II, III, IV and V Cl. Ost. Gin. Univ. Milano; I and II Cl. Ost. Gin. Univ. Torino; Cl. Ost. Gin. Univ. Genova, Pavia and Padua; I and II Cl. Ost. Gin. Univ. Bologna; Cl. Ost. Gin. Univ. Cattolica S. Cuore di Roma, Ist.

Regina Elena, Roma, II Cl. Ost. Gin. Univ. Roma; I and II Cl. Ost. Gin.. Univ. Bari; Cl. Ost. Gin. Univ. Pisa, Catania, Florence.

After a further discussion, a common data base has been agreed upon and a modular chart for the collection of data has been elaborated and printed. A six-month pilot study is to be started February 1, 1980.

437. STUDIES OF PATIENTS WITH DISSEMINATED SOLID TUMORS

Canellos, G. P., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts,* 02115, United States of America

Independently and not as an agent of the Government, the Contractor shall exert its best efforts to conduct Phase II and Phase III Studies in Patients with Disseminated Solid Tumors. The tumors to be included in these studies shall be limited to the following: Large bowel cancer, bronchogenic cancer, malignant lymphoma, head and neck cancer, endometrial cancer, ovarian cancer, bladder cancer, soft tissue cancer, breast cancer, prostate cancer, bone sarcoma. A minimum of 400 patients shall be included in these studies with no fewer than 25 patients from any one tumor type group.

D. THERAPY OF MULTIPLE GYNECOLOGICAL CANCERS

438. CHEMOIMMUNOTHERAPY OF INOPERABLE CANCER OF THE VULVA

Silveira, J. G., Almeida, A. B., Silveira, G. G., Bolognesi, L. T., Pontificia Universidade Catolica do Rio Grande do Sul, School of Medicine, Dept. of Obstetrics & Gynecology, *Avda. Ipiranga 6681. Caixa Postal 1429, Porto Alegre 90000, Brazil*

OBJECTIVE: To improve the local conditions of the inoperable epidermoid carcinoma of the vulva, by reducing the ulceration and the edema and, thereby, to improve the urinary and rectal functions; to develop the use of immunotherapy as an adjuvant to chemotherapy.

APPROACH: All patients with proved epidermoid carcinoma of the vulva without conditions of operability are submitted to a four-drug five-day chemotherapy: Day 1: Bleomycin, 15 mg; Day 2: Vincristine, 1 mg/m2; Day 3: Cyclophosphamide, 400 mg, plus Methotrexate, 50mg; Day 4: Cyclophosphamide, 400 mg; and Day 5: Cyclophosphamide, 400 mg.

All drugs are injected intravenously and the treatment is repeated after a 3-week interval. If an objective response is obtained after three treatments (reduction of 50% of the ulceration or of the exophytic tumor), the protocol is continued for one year. All patients suitable for this protocol are randomized, every other patient receiving 150 mg of levamisole on days 2, 3, 4, 16, 17 and 18 of the interval.

439. CANCER OF THE VULVA - CLINICAL ASPECTS, EARLY DIAGNOSIS AND TREATMENT

Briones, R. H., Dabancens, A., Universidad de Chile, Jose Joaquin Aguirre Clinical Hospital, Dept. of Binecologia, *1058 Av. Bernardo O'Higgins, Santiago, Chile*

OBJECTIVES: To perform a clinical study of cancer of the vulva. To study premalignant lesions of the vulva.

APPROACH: Referral of patients from the specialized practice, begun in 1963, of 'Diseases of the Vulva' within the Hospital Clinico of the University of Chile.

Histologic study in the University of Chile's Laboratory for the Department of Obstetrics and Gynecology, in collaboration with Dr. Dabancens.

Study of estrogen receptors in the vulvar tissue in patients with carcinoma or premalignant lesions of the vulva, in collaboration with Dr. R. Guerrero of the Biochemistry Laboratory of the Department of Obstetrics and Gynecology, University of Chile.

Surgical treatment of patients with in situ carcinoma of the vulva. Resection plus simultaneous plastic surgery.

Progress: Periodical reports to the Chilean Society of Obstetrics and Gynecology and the Congress of the International Society for the Study of Vulvar Disease, Montbazan, France, May 1978.

440. TOPICAL CHEMOTHERAPY FOR VULVAR NEOPLASMS (HUMAN)

LaGasse, L. D., University of California, Los Angeles Campus, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California,* 90024, United States of America

This is part of a broader project. A summary of this subproject is not available.

441. TREATMENT OF ADVANCED GYNECOLOGICAL MALIGNANCIES

Brenner, D. E., Aisner, J., Wiernik, P. H., Konits, P., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Medical Oncology, *Baltimore, Maryland,* 21201, United States of America

Although alkylating agents are active, combination chemotherapy is superior to single agent therapy in patients with advanced ovarian cancer. Doxorubicin and cis-platinum is an active combination. VP16-213 has activity in male germinal tumors. The combination of cis-platinum, doxorubicin, cyclophosphamide and VP16-213 creates the possibility of multiple synergistic pairs. This four-drug combination is therefore studied for the treatment of advanced epithelial tumors of the ovary. Two patients have been entered into study. There is suggestion of antitumor activity with partial responses in both patients who had advanced high grade tumors. It is too early to evaluate for response or toxicity.

Salvage chemotherapy in patients with ovarian carcinoma, endometrial carcinoma, or cervical carcinoma rarely exceeds 10% to 20% response rates. In the current study 22 patients with advanced gynecologic malignancies (8 ovary, 9 cervix, 2 endometrial, and 3 adenosquamous) have been treated with 120 mg/m2 of mAMSA. Two partial responses, one in endometrial carcinoma and one in cervical carcinoma, have been observed in 20 evaluable patients. It is still too early to evaluate level of activity since at least 15 patients per tumor type are needed to exclude a 20% possibility of activity.

442. PROGRAMMED CHEMOTHERAPY AND CELL KINETICS IN GYNECOLOGIC CANCER

Averette, H. E., University of Miami, School of Medicine, Dept. of Oncology, *1400 N.W. 10th Ave., Box 520875, Coral Gables, Florida,* 33152, United States of America

This is part of a broader project. A summary of this subproject is not available.

443. RADIATION THERAPY AND BIOLOGY RESEARCH PROGRAM

Fischer, J. J., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

Clinical studies in advanced carcinoma of the head and neck region, Hodgkin's disease and non-Hodgkin's lymphomas, carcinoma of the breast, gastrointestinal cancer, gynecologic malignancies, prostatic cancer and radiation dose rate effects on the hematopoietic system are continued and new studies are planned.

Radiological physics research includes: magnetic control of the dose distributions produced by high energy electron beams, calorimetric determination of dosimetric parameters and general medical physics.

Laboratory investigations include: experimental radiation therapy of rodent solid tumors, radiation reaction preventive agents and normal tissue response, the response of vascular endothelium to ionizing radiation, NMR detection of hypoxic cells, the influence of the red blood cell concentration of 2,3-diphosphoglycerate on the radiation response of the rat rhabdomyosarcoma R1112.

Our investigations also include: enzymatic mechanisms in postreplication repair; study of error-prone DNA repair pathways in mammalian cells, study of herpes virus genome structure site specific mutagenesis in gene for thymidine kinase of herpes simplex virus; molecular mechanisms of DNA repair in E. coli, hypoxic radiosensitizers: structure-function relations and mechanisms of sensitization and toxicity; analysis of gene function involved in genetic recombination in E. coli; site directed mutagenesis, role of secondary structure in gene regulation; cell proliferation in EMT6 tumors and examination of new agents for altering the radiation response of solid tumors.

444. STUDIES IN PATIENTS WITH DISSEMINATED SOLID TUMORS

Baker, L. H., Wayne State University, School of Medicine, Dept. of Oncology, *1014 Rivard, Detroit, Michigan,* 48207, United States of America

OBJECTIVE: Conduct Phase II and Phase III studies in patients with solid disseminated tumors. Tumors to be included in these studies will be limited to: lung carcinoma; ovarian carcinoma; cervical carcinoma; endometrial carcinoma; head and neck carcinoma; prostatic carcinoma; bladder carcinoma; and melanomas and sarcomas of soft tissue. A minimum of 400 patients will be included in these studies with no fewer than 25 patients from any one tumor type group. All patients will be treated intensively with chemotherapy either alone or in combination with other drugs, radiotherapy, immunotherapy, or surgery.

445. RECURRENT CANCER AND ITS PSYCHOSOCIAL CONSEQUENCES

Weisman, A. D., Worden, J. W., Massachusetts General Hospital, Psychiatry Service, *32 Fruit St., Boston, Massachusetts,* 02114, United States of America

The purpose of this study is: 1) to evaluate the psychosocial characteristics of patients with recurrent cancer, 2) to identify those recurrent patients who are at highest risk for emotional distress and poor coping, and 3) to test a screening procedure and two different short-term interventions which previously were proven effective in newly diagnosed patients. Our central hypothesis is that recurrence is more distressing than diagnosis of cancer and that appropriate interventions can significantly reduce levels of distress and fortify coping strategies, especially in case of patients screened as high risk.

Patients from the following cancer site groups will be studied: breast, colon, lung, malignant melanoma, Hodgkin's disease, female reproductive organs (cervix, ovary, uterus), and male genitourinary system (bladder, prostate, testes). These sites offer a wide variety of malignancies, prognoses, treatment modalities, and psychosocial issues. Patients will be assigned to one of three groups, two groups receiving intervention and one a non-intervened control group. Patients will be assessed through interview, rating scales, and psychological testing within the first month of recurrence and then at 2, 4, and 6 months post-recurrence. Interventions will take place following the initial assessment and will continue over a 4-week time period.

446. COUNSELING CANCER PATIENTS IN COPING STRATEGIES

Houts, P. S., Miller, R. W., Curry, S. L., Pennsylvania State University, Milton S. Hershey Medical Center, School of Medicine, Dept. of Behavioral Science, *500 University Dr., Hershey, Pennsylvania,* 17033, United States of America

The fact that many cancer patients experience considerable psychological stress as a result of their illness is well-known and documented. Weisman and Worden (1977) as well as other investigators have shown that anxiety and depression are common and frequently peak within the first six weeks of treatment. This study proposes to counsel a group of gynecologic cancer patients during the six weeks following initial diagnosis and to test whether anxiety and depression are lessened as a result. The counseling techniques to be used include having the patient view videotapes where successfully adapting cancer patients will model (demonstrate) coping strategies which have helped them control their anxiety and depression. Coping strategies will include those identified as effective in earlier research on coping in cancer patients. Counselors will help each patient identify those coping strategies which would be most appropriate and helpful for her and to set individual goals for using these strategies in everyday life.

Modeling and goal setting have been shown to be effective counseling techniques for reducing anxiety and depression in patients with a wide range of medical problems. This study is unique in that it systematically applies these counseling techniques to the treatment of anxiety and depression in cancer patients.

Two control groups will be utilized: 1) a group who receive standard treatment by the gynecologic oncology clinic staff, including individual attention to their psychological needs as they arise, and 2) a group who receive standard clinic treatment as in 1) above, plus attendance at an information group. Group 2) will assess the effects of receiving additional attention but without individualized counseling, modeling and goal setting which occur in the experimental group.

E. MEMBERS OF GYNECOLOGIC ONCOLOGY GROUP

447. GYNECOLOGIC ONCOLOGY GROUP

Shingleton, H. M., Hatch, K. D., Taylor, P. T., Levy, D. S., University of Alabama in Birmingham, School of Medicine, Dept. of Obstetrics & Gynecology, *1919 7th Ave. S., Birmingham, Alabama,* 35233, United States of America

The University of Alabama in Birmingham has been a member of the Gynecologic Oncology Group since its inception in 1971. The objectives of the Group and the details of the study protocols are described in Group Chairman's application. As one of the most active of the member institutions, Alabama participates in most of the ongoing protocol studies and has accessioned well over three hundred patients to date.

Following a time reassessment and reorganization, this unique interdisciplinary group has activated many new protocol studies and upgraded data collection methods, making available to the investigators studies for almost all gynecologic malignancies in early and late stages. At this institution, affiliation with the Huntsville Hospital in North Alabama has extended the GOG protocols to satellite areas one hundred miles distant from Birmingham. The University of Alabama has a unique opportunity of providing comprehensive care to large numbers of indigent patients and continuing education to physicians throughout the state and area. The presence in the Birmingham metropolitan area of five gyn. oncologists is extraordinary and thus efforts to improve care of cancer patients through prospective studies of the GOG have great promise.

448. GYNECOLOGIC CANCER EDUCATION

Shingleton, H. M., Gore, H., Younger, J. B., Taylor, P. T., Hatch, K. D., Austin, J. M., University of Alabama in Birmingham, School of Medicine, Dept. of Obstetrics & Gynecology, *1919 7th Ave. S., Birmingham, Alabama,* 35233, United States of America

This is a continuation of a grant to develop a communications educational network to improve cancer detection, treatment and referral patterns in Alabama. It involves colposcopy clinics, manned by local physicians, nurse practitioners trained in educational methods and patient counselling, and a physician education, patient management program for women with trophoblastic disease.

449. UNIVERSITY ONCOLOGY PROGRAM

Bagshaw, M. A., Rosenberg, S. A., Martinez, A., Coleman, C. N., Jacobs, C., Kempson, R., Fee, W., Stockdale, F., Sikic, B., Stanford University, School of Medicine, Dept. of Radiology, *Stanford, California,* 94305, United States of America

This proposal is for the continuation of Stanford participation in the Northern California Oncology Group (NCOG) for a multi-institutional cooperative study of the multi-modality treatment of a variety of neoplasms. The multi-modality studies will include various combinations of surgery, radiation therapy, and chemotherapy, used either as adjuvants or as primary treatment in carcinoma of the breast, bronchus, gastrointestinal tract, urinary bladder, prostate, non-seminoma-testicular neoplasms, ovarian carcinoma, cervical carcinoma, endometrial carcinoma, epidermoid carcinoma of the head and neck and melanoma. Stanford intends to participate in almost all of the active programs which, it is estimated, will number about 30 at any given time. Special features of the Stanford participation will include an extramural network of participating medical oncologists, the use of our oncology day care center for the administration of chemotherapeutic agents on an out-patient basis and the use of our clinical research center (CRC) for in-patient hospitalization in support of protocols approved by the CRC advisory board. In addition to clinical participation Stanford intends to use its radiobiology facilities for further studying radiotherapeutic and chemotherapeutic interactions, hyperthermia, and radiation sensitizers.

450. GYNECOLOGIC ONCOLOGY PROGRAM

Morrow, C. P., Schlaerth, J. B., Nalick, R. H., Wallace, D., Yordan, E., Gaddis, O., O'Brien, T. J., University of Southern California, School of Medicine, Dept. of Obstetrics & Gynecology, *2025 Zonal Ave., Los Angeles, California*, 90033, United States of America

The LAC/USC Gynecologic Oncology Division is one of the largest and most active in the country. The objectives of this project are to facilitate the division activities in the areas of cancer screening and outreach; cancer education; and cancer research through the mechanism of grant support for administrative, professional and secretarial personnel. The goals for the current year are to complete the development of a protocol for diagnosis and treatment of the common gynecologic cancers. This will be made available to tumor boards and physicians. The educational and outreach programs will be continued at their present level. Our cancer research projects on hormone receptors in endometrial cancer will be extended to selected neighboring community hospitals. A collaborative study with the Jet Propulsion Laboratory on the analysis of two-dimensional maps of tumor proteins is planned.

BIBLIOGRAPHIC REFERENCES: DiSaia, P.J., Morrow, C.P., Hill, A. and Mittelstaedt, L.: Immune competence and survival in patients with advanced cervical cancer - peripheral lymphocyte counts. Am. J. Roentgenol., 1978. Kletzky, O.A., Scott, J. Z., Morrow, C.P. and Mishell, D.R.: A comparative study between radioreceptor assay and radioimmunoassay for hCG in patients with trophoblastic disease. Obstet. Gynecol. 52:328, 1978.

451. GYNECOLOGIC ONCOLOGY GROUP

Morrow, C. P., Bernstein, S., d'Ablaing, G., Gaddis, O., Hernandez, W., Nalick, R. H., O'Brien, T. J., Schlaerth, J. B., Shen, J., Stowe, S., University of Southern California, Los Angeles County General Hospital, Dept. of Obstetrics & Gynecology, *3551 University Ave., Los Angeles, California*, 90007, United States of America

The Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Southern California, is a full member of the Gynecologic Oncology Group. The overall goals of the GOG and its study protocols are described in the Group Chairman's grant application.

452. GYNECOLOGIC ONCOLOGY GROUP

LaGasse, L. D., Castaldo, T. W., Petrilli, E. S., University of California, Los Angeles Campus, School of Medicine, Dept. of Obstetrics & Gynecology, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

Under the auspices of the UCLA membership, five Los Angeles hospitals participate in the clinical research efforts of the Gynecologic Oncology Group. The contribution of the UCLA network represents one of the largest patient accession rates in the cooperative group. The quality of the UCLA network participation is well above the established standards.

From a gynecologic patient population of over 550 new invasive cases per year, these institutions can be expected to accession a minimum of 100 protocol patients annually. An average of 43% of these can be predicted to be in the 'high priority' protocols which represent the major emphasis of the GOG.

453. GYNECOLOGIC ONCOLOGY GROUP

DiSaia, P. J., Rich, W. M., Freeman, R. K., Ostergard, D. R., Carney, P., Colman, M., Rao, Y., Austin, P., Armentrout, S., University of California, Irvine Campus, California College of Medicine, Dept. of Obstetrics & Gynecology, *Irvine, California*, 92664, United States of America

Our institution (University of California, Irvine, College of Medicine and affiliated hospitals) is a new member of the Gynecologic Oncology Group. The overall goals of the Group and the study protocols are described in the Group Chairman's grant application.

The Division of Gynecologic Oncology, Department of Gynecology and Obstetrics, College of Medicine, University of California, Irvine and its affiliated hospitals will conduct the clinical studies. The two major institutions involved in the accession of patients to protocol will be: California College of Medicine, University of California, Irvine, Dept. Gyn/Ob, 101 City Drive South, Orange, California, 92668, and Women's Hospital, Memorial Medical Center, 2801 Atlantic Blvd., Long Beach, California, 90801.

Our institution will register all new gynecological cancer patients entering our hospitals with the Group Operations Office and will participate in the following Group studies: Protocols Nos. 13, 14, 20, 22, 24, 25, 26 (C-H), 28, 29, 31, 32, 33, 34, 36, 37, 40, 41, 42, 43, 44, 45, 46, 47, 7601 and 7602, and 284 cases are estimated yearly for grant period 1980 through 1985.

454. GYNECOLOGIC ONCOLOGY GROUP

Major, F. J., Colorado Regional Cancer Center Inc., Obstetrics & Gynecology Service, *1655 Lafayette St., Suite 301, Denver, Colorado*, 80218, United States of America

Our institution is a member of the Gynecologic Oncology Group. The overall goals of the Group and the study protocols are described in the Group Chairman's grant application. We will enter 30-40 patients on protocol studies annually.

Our institution will register all new gynecologic cancer patients entering our hospital with the Group Operations Office (number of cases expected annually is 75).

The institution has recently approved dissemination of GOG Protocols to gynecologists, oncologists and radiotherapists throughout the CRCC region. Protocol entries are beginning to come from outlying hospitals in the region and are expected to increase. CRCC Outreach Activities are now providing consultation to physicians throughout the region and, thus, supervised participation in protocols is available to all interested physicians in the region.

455. GYNECOLOGIC ONCOLOGY GROUP

Delgado, G., Kurman, R., Hill, L. T., MacDonald, J., Walker, W. P., Georgetown University, School of Medicine, Dept. of Obstetrics & Gynecology, *3800 Reservoir Rd. N.W., Washington, District of Columbia*, 20007, United States of America

Georgetown University and Affiliated Hospitals is a member of the Gynecologic Oncology Group under the direction of Dr. Gregorio Delgado, the Principal Investigator. The overall goals and objectives of the Gynecologic Oncology Group are the improved diagnosis and treatment of patients with gynecologic malignancies and are further detailed in the Group Chairman's Grant Application.

As a member of the Gynecologic Oncology Group, our institution will register all new patients with gynecologic malignancies (an expected 250 cases annually) treated in the Georgetown University Affiliated Hospitals with the Group Headquarters. We will also actively participate in the treatment protocols as listed in Appendix No. 1. Another goal of our institution will be to assist in the evaluation of data obtained in these studies.

456. GYNECOLOGIC ONCOLOGY GROUP

Park, R. C., Heller, P., Lee, R., Blom, J., Weisbaum, G., Neglia, W., Leman, M., Hoskins, W. J., U.S. Dept. of Defense, Army, Medical Research & Development Command, Walter Reed Army Inst. of Research, Dept. of Obstetrics & Gynecology, *Washington, District of Columbia*, 20012, United States of America

Nine years ago Walter Reed Army Medical Center joined with other members in a cooperative Gynecologic Oncology Group for the purpose of conducting joint clinical investigation in gynecologic oncology.

This group has undertaken clinical trials and other cooperative studies in an endeavor to advance knowledge in the curative and palliative management of gynecologic cancer. Through the collaboration of radiation therapy centers and gynecologic oncology centers joined in the Gynecologic Oncology Group, it has been and will continue to be possible to provide an adequate number of patients to answer significant questions in the treatment of gynecologic tumors.

Currently we are involved in treatment protocols designed to study invasive vulvar carcinoma, cervical dysplasia, and advanced cervical carcinoma, as well as all stages, primary and recurrent, of ovarian carcinoma, endometrial carcinoma and uterine sarcoma.

457. GYNECOLOGIC ONCOLOGY GROUP - HEADQUARTERS

Lewis, G. C., Brady, L., Blessing, J., American College of Obstetricians & Gynecologists, Dept. of Obstetrics & Gynecology, *1*

E. Wacker Dr., Suite 2700, Chicago, Illinois, 60601, United States of America

Clinical trials in gynecologic oncology will be continued by a multi-discipline group using Phase II and Phase III protocols. New drug screening for all gynecologic tumor types, pilot studies and the results of Phase III studies will continue to serve as principal sources for new randomized trial programs evaluating chemotherapy, irradiation, surgery, immunotherapy and cervical pathology. Every phase and stage of gynecologic malignancy will be included in these protocols, and markers for tumors and other critical parameters will be sought out and tested to see if they can be used as guideposts to the most effective therapy in future studies.

458. DEVELOPMENT OF COORDINATED CANCER PROGRAM

Steiner, J. W., Illinois Cancer Council, *36 S. Wabash Ave., Suite 700, Chicago, Illinois,* 60603, United States of America

The Illinois Cancer Council proposes to create among existing cancer control resources in Illinois, a regionalized system of planning, administration, statistical evaluation and service activities for the control of cancer in identified populations. The objectives include demonstration of superior productivity of interinstitutional collaboration when impacting large populations. Model regional subsystems being created are targeted to: the community-based nursing care and appropriate tertiary site liaisons for pediatric oncology patients; formally integrating physicians and their gynecologic oncology patients in community hospitals into clinical and educational programs which traditionally were fully exploitable only in large medical school centers where they have been based; and to study the needs of cancer patients particularly in rehabilitation, in order that sound bases for future plans for delivery of services can be accomplished.

459. ILLINOIS CANCER COUNCIL - GYNECOLOGIC ONCOLOGY GROUP

Wilbanks, G. D., Illinois Cancer Council, *36 S. Wabash Ave., Suite 700, Chicago, Illinois,* 60603, United States of America

The objective of this proposal is to develop a regional cooperative group to conduct gynecologic oncology clinical research through the participation of the Illinois Cancer Council Gynecologic Oncology Group (ICC-GOG) in the Gynecologic Oncology Group (GOG). By utilizing the services of the centralized ICC Protocols Office, the ICC-GOG will be able to collect and evaluate data of uniform high quality. It is anticipated that such research and GOG participation will be performed at the same or lower cost than a dispersed network of the same size.

The institutions currently involved are Illinois Comprehensive Cancer Center, Rush-Presbyterian-St. Luke's Medical Center, St. Francis Hospital, University of Chicago-Chicago Lying-In, Cook County Hospital, Northwestern University-Prentice Women's Hospital, Michael Reese Hospital and Medical Center.

The University of Illinois Hospital is expected to join the ICC-GOG in July 1979, and Columbus, St. Joseph's and Resurrection Hospitals are expected to join later in 1979-1980.

460. GYNEOLOGIC ONCOLOGY GROUP

Ehrlich, C. E., Indiana University - Purdue University at Indianapolis, School of Medicine, Dept. of Obstetrics & Gynecology, *1219 W. Michigan St., Indianapolis, Indiana,* 46202, United States of America

The purpose of this project is to improve results of treatment for women who have pelvic cancer by development of more effective means for prevention, detection, diagnosis, therapy, and follow-up. It is proposed that this be done within the Gynecologic Oncology Group which is a multi-disciplinary organization consisting of gynecologists, pathologists, medical oncologists, immunotherapists and radiation oncologists who are especially oriented toward clinical investigation. In this project gynecologic malignancies will be treated utilizing a multi-disciplinary approach using protocols formulated by the Gynecologic Onology Group. The goals are to improve patient care, prolong survival, and rapidly assess new treatment methods for women with gynecologic malignancies. Another important goal is the dissemination of knowledge and skill gained through this research to the clinical practitioners and thus to their patients with pelvic malignancies.

461. GYNECOLOGIC ONCOLOGY GROUP

Lifshitz, S., Platz, C., Tewfik, H., Clamon, G., University of Iowa, School of Medicine, Dept. of Obstetrics & Gynecology, *Jessup Hall, Iowa City, Iowa,* 52240, United States of America

The Gynecologic Oncology Group represents a national collaborative effort in gynecologic cancer. It is a multidisciplinary group, involved primarily in clinical therapeutic trials in the treatment of female genital cancer. In addition, some nontherapeutic pathology and registry studies are being conducted.

The objectives, methods and research goals of the Gynecologic Oncology Group are described in detail in the GOG chairman's research project application.

462. AN EXPERIMENTAL MULTIMODALITY PROGRAM IN OVARIAN CANCER

Order, S. E., Colvin, M., Durand, R. E., Rosenshein, N., Hilton, J., Johns Hopkins University, School of Medicine, Dept. of Radiation Oncology, *725 N. Wolfe St., Baltimore, Maryland,* 21205, United States of America

Recent information concerning the pathophysiology of ovarian cancer, including patterns of dissemination of biomarkers as well as new techniques of irradiation, has been combined into a new investigative and clinical program.

In the experimental laboratory the pharmacokinetics of drug metabolism and resistance of alkylating agents such as adriamycin and others are being evaluated in vitro and in vivo.

The cell kinetics of ovarian cancer, both experimental and clinical, are being examined and the radiosensitivity determined.

In the clinical program colloidal P32, delayed split abdominal irradiation, antisera, and chemotherapy are being utilized. A disciplined staging system has yielded important staging data and the preliminary 4-year survival statistics are encouraging.

463. SOUTHWEST ONCOLOGY GROUP

Baker, L. H., Wayne State University, School of Medicine, Dept. of Oncology, *1014 Rivard, Detroit, Michigan,* 48207, United States of America

Wayne State University is the leading contributor of patients to Southwest Oncology Group protocols. In five of the thirteen committees of the group, Wayne State has contributed ten percent or more of the total population of patients studied by that group. These committees include: Brain (22%), GI (12%), GYN (10%), Lung (10%), Sarcoma (13%).

Wayne State University is represented on each disease committee of the adult division by member medical oncologists, pathologists, surgeons or radiation therapists.

Members of the department are chairing (or co-chairing) the following major southwest studies: Dr. Samson, 7817 testicular study; Dr. Baker, 7613 sarcoma study; Dr. Al-Sarraf, 7727/28 melanoma study; Dr. Samal, 7725 breast study; Dr. Buroker, new first line Phase II-III large bowel study. Other Phase II studies being chaired by faculty members include: Dr. Samson, 7611 Platinum in Sarcomas; Dr. Voravit, 7821 Maytansine in Lymphomas; Dr. Al-Sarraf, 7730 Platinum in Melanoma and 7716 Tamoxifen in Renal Cancer; Dr. Baker, 7870 Mitomycin and Bleomycin in Cervical Cancer.

The WSU faculty hold leadership roles in Southwest Oncology Group administration. Dr. Vaitkevicius and Dr. Buroker are Chairman and Vice-Chairman of the GI Committee, Dr. Baker is Chairman of the Sarcoma Committee, a member of the Executive Committee of the Adult Division, serves on the Steering Committee of GYN Committee and is a representative to the Pharmacology Committee.

BIBLIOGRAPHIC REFERENCES: Baker, L.H., Opipari, M.I., Wilson, H., Bottomley, R., and Coltman Jr., C.A. Mitomycin C, Vincristine and Bleomycin Therapy for Advanced Cervical Cancer. Obstetrics and Gynecology, 52: 146-150, 1978. Benjamin, R.S., Baker, L.H., O'Bryan, R.M., Moon, T.E., and Gottlieb, J.A. Chemotherapy for Metastatic Osteosarcoma - Studies by the M.D. Anderson Hospital and the Southwest Oncology Group. Cancer Treatment Reports 62: 237-238, 1978.

464. GYNECOLOGIC ONCOLOGY GROUP

Prem, K. A., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Obstetrics & Gynecology, *1305 Mayo, Minneapolis, Minnesota,* 55455, United States of America

The objectives of the proposed study are to participate as a cooperative member of the Gynecologic Oncology Group, performing clinical cooperative trials in solid tumors. Investigations will include a variety of Phase I, Phase II, and Phase III studies in patients with gynecologic malignancies using chemotherapy, radiation therapy, surgical therapy and combinations of these modalities. Adjuvant therapeutic trials are specifically planned for: 1) adenocarcinoma of the endometrium, 2) adenocarcinoma of the ovary, 3) uterine sarcoma, 4) squamous cell carcinoma of the vulva, 5) advanced, recurrent pelvic malignancy.

465. GYNECOLOGIC ONCOLOGY GROUP

Thigpen, J. T., Wiser, W. L., Mladineo, J., Boronow, R. C., Anis, O., Hickman, B. T., Ricketson, G., Tai, D., Evers, C. G., University of Mississippi, Medical Center, School of Medicine, Dept. of Obstetrics & Gynecology, *2500 N. State St., Jackson, Mississippi*, 39216, United States of America

Clinical research in the field of gynecologic oncology has assumed an improved quality and credibility through the recent efforts of the Gynecologic Onocology Group. Whereas previous efforts at defining prognostic variables for gynecologic neoplasms largely dealt with small groups of patients who were inadequately staged, the validity of careful surgical pathological staging in gynecologic cancer is achieving acceptance as a result of such trials involving large numbers of patients entered on GOG studies. A similar lack of properly designed, properly controlled trials of a combined modality approach to the treatment of gynecologic cancer has been at least partially corrected by recent GOG studies which meet the criteria for proper protocol design and control. Less studied neoplasms such as endometrial carcinoma have received new emphasis within the GOG. Furthermore, a concerted effort at identification of new active chemotherapeutic agents and a logical approach to development of effective combination of these agents in the treatment of gynecologic cancer has been undertaken within the GOG. These current accomplishments of the GOG vindicate a multi-institution, collaborative approach to clinical research in gynecologic oncology to which the University of Mississippi School of Medicine is committed. This institution plans to expand participation within the Gynecologic Oncology Group (GOG) in 4 specific areas: (1) entry of cases onto groupwide protocols, (2) participation studies, (3) input into the scientific design of studies, and (4) group committee work dealing with protocol development and group administration. Current input is significant in all 4 of these areas as is documented in this application.

BIBLIOGRAPHIC REFERENCES: Thigpen, T., LaGasse, L., and Bundy, B.: Phase II Trial of Cis-Platinum in Treatment of Advanced Ovarian Adenocarcinoma. In Press in Proc. AACR 1979. LaGasse, L., Thigpen, T. and Morrison, F.: Phase II Trial of Piperazinedione in Treatment of Advanced Endometrial Carcinoma, Uterine Sarcoma, and Vulvar Carcinoma. In Press in Proc. ASCO 1979.

466. GYNECOLOGIC ONCOLOGY GROUP

Smith, M. L., University of Nebraska, Medical Center, School of Medicine, Dept. of Obstetrics & Gynecology, *42nd & Dewey Aves., Omaha, Nebraska*, 68105, United States of America

Our institution became a Provisional Member of the Gynecologic Oncology Group in February 1977, and we are actively participating in 15 protocols and anticipate participating in 7 of the new protocols after they have been approved by our institutional Human Investigation Committee.

Our institution will register with the Group's Statistical Office (all new gynecologic cancer patients). During the last calendar year we saw 108 new patients with invasive gynecologic malignancies. We predict that this number will increase and that 30 patients will be enrolled on protocols this coming year.

The undersigned agrees to accept responsibility for the scientific and technical conduct of the product and for the provision of required progress reports if a grant is awarded as a result of this application.

467. EASTERN COOPERATIVE ONCOLOGY GROUP

Kaplan, B. H., Vogl, S. E., Escher, G., Volk, H., Ghossein, N., Janis, M., Axelrod, M., Campbell, P., Greenwald, E., DiPillo, F., Geraty, M., Camacho, F., Yeshiva University, Bronx Campus, Albert Einstein School of Medicine, Dept. of Medicine, *1300 Morris Park Ave., Bronx, New York*, 10461, United States of America

The Albert Einstein College of Medicine will continue to participate in the activities of the Eastern Cooperative Oncology Group, in all phases. AECOM will put substantial numbers of patients into groupwide cooperative trials; it will design and carry out pilot studies to test new regimens for possible groupwide application, and members of its faculty will assist in committee activities for the ECOG.

Investigators from AECOM are directing groupwide trials in head and neck carcinoma, ovarian cancer, and small cell cancer of the lung. AECOM remains the largest contributor of patients to approved ECOG-pilot studies. Currently pilot studies are underway in esophageal, cervical, head and neck, and ovarian cancer, and proposals for new pilot studies in breast, gastric and colorectal cancer are under consideration.

BIBLIOGRAPHIC REFERENCES: Vogl, S., Kaplan, B. Chemotherapy of Advanced Head and Neck Cancer with Methotrexate, Bleomycin, and Cis-diamminedichloroplatinum II in An Effective Outpatient Schedule, Cancer, 44:26-31,1979. Vogl, S., Zaravinos, T., Kaplan, B. Toxicity of Cis-diamminedichloroplatinum II Given in a Two-Hour Outpatient Regimen of Diuresis and Hydration, Cancer, 45: 11-15, 1980.

468. GYNECOLOGIC ONCOLOGY GROUP

Rotman, M., New York Medical College, Manhattan Campus, School of Medicine, Dept. of Obstetrics & Gynecology, *1249 5th Ave., New York, New York*, 10029, United States of America

OBJECTIVES: To form a group of collaborating institutions to engage in joint clinical investigations in Gynecologic Malignancy. Cooperative studies will be undertaken to advance knowledge in the curative and palliative management of gynecologic malignancy. Through the combined efforts of the gynecologic oncologists, radiotherapists, pathologists, immunologists and medical oncologists and conducting a cooperative study it may be possible to provide an adequate number of patients to answer significant questions in the treatment of cancer, not previously answerable by any single institutional study.

This group will collect long-term data with regard to epidemiology, patient survival, and complications resulting from various treatment plans. The group will be a cooperative multidisciplinary and multi-institutional venture which integrates study programs in gynecologic cancer and will enrich training programs in gynecologic and medical oncology and radiation therapy.

469. GYNECOLOGIC ONCOLOGY GROUP

Beecham, J. B., University of Rochester, School of Medicine & Dentistry, Dept. of Obstetrics & Gynecology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

Our major objective is to broaden physician and patient participation in clinical protocols of the Gynecologic Oncology Group, through a collaborative approach toward the care of women with gynecologic malignancies. We will emphasize four basic approaches. The first two involve continuation of didactic lectures within the city of Rochester and the nine counties that form the cachement area of the University of Rochester Cancer Center and the Division of Gynecologic Oncology and maintenance of our present level of tumor board participation, with an anticipated increase in coverage of the Rochester tumor conference and, as political realities are explored, tumor conferences of some of the closer surrounding hospitals in the region. Currently, we supervise the gynecological oncology conferences at the Strong Memorial Hospital, the Genesee Hospital, and the Arnot-Ogden Memorial Hospital in Elmira, New York, with active participation in the weekly Highland Hospital Conference. Thirdly, we look for increased participation of our oncology nurse; currently her part-time status is supported through a Cancer Control Contract. Full funding would afford a greater involvement with our own Service and improve monitoring of case accessions and quality control of chemotherapy in outlying hospitals. Fourthly, funding for the medical oncology units at the surrounding Rochester hospitals will enable any woman with gynecologic cancer to be treated through the most appropriate cooperative oncology group protocol available for her specific stage and diagnosis. We have been assured that few if any patients will be lost to GOG Protocol accession, and no patients will be treated with other cooperative Group Protocols if GOG Protocols are the most appropriate.

470. GYNECOLOGIC ONCOLOGY GROUP

Creasman, W. T., Weed, J. C., Gall, S. A., Hammond, C. B., Parker, R. T., Currie, J. L., Clark Pearson, D., Fetter, B. F., *Woodward, K. T.*, Duke University, School of Medicine, Dept. of Obstetrics & Gynecology, *Box 3711, Durham, North Carolina*, 27710, United States of America

The Headquarters Office of the Gynecologic Oncology Group (GOG) under the direction of the Chairman, Dr. Goerge Lewis, in submission of the renewal grant has stated the objectives, goals and progress of the group. As an active member of the GOG, the Gynecologic Oncology Division of the Department of Obstetrics and Gynecology of the Duke University Medical Center endorses those objectives and goals.

471. GENERAL CLINICAL CANCER RESEARCH CENTER

Laszlo, J., Seigler, H. F., Huang, A. T., Fay, J., Reisner, E., Fyfe, M. J., Metzgar, R. S., Cohen, H. J., Briner, W., Joines, W., Hanker, J., Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina*, 27710, United States of America

This is the third year of the present Program Project Grant to study diagnosis, prognostic factors, and therapy of malignant disease. The Clinical Project Programs cover projects concerning head and neck cancer, acute and chronic leukemia, malignant melanoma, leukemia and melanoma immunology, breast cancer, prostate cancer, gynecologic tumors and brain tumors.

The focal point for this research is a new clinical cancer building which includes a 20 bed cancer research ward and outpatient facilities for multidisciplinary clinics. A series of these clinics have been created to reflect the combined input of medical and surgical oncologists, radiation therapists and support personnel such as nurse-oncologists, pharmacists and social workers.

472. GYNECOLOGIC ONCOLOGY GROUP

Fowler, W. C., Walton, L. A., University of North Carolina, Chapel Hill Campus, School of Medicine, Dept. of Obstetrics & Gynecology, *Manning Dr., Chapel Hill, North Carolina*, 27514, United States of America

The Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, is a member of the Gynecologic Oncology Group (GOG). This is an interdisciplinary group made up of over 30 institutions to investigate the therapeutic measures for patients with gynecologic cancer. The details of the study protocols are described in the Group Chairman's grant application. Our institution is registering all new gynecologic oncology patients with the Group Operations Office. We are participating in many of the ongoing funding and in the introduction of new protocols.

473. GYNECOLOGIC ONCOLOGY GROUP

Homesley, H. D., Jobson, V. W., Muss, H. B., Bullock, M. S., Marshall, R. B., Gusdon, J. P., Wake Forest University, Bowman Gray School of Medicine, Dept. of Obstetrics & Gynecology, *300 S. Hawthorne Rd., Winston Salem, North Carolina*, 27103, United States of America

The primary objective of the Gynecologic Oncology Group is to improve the treatment results in patients with gynecologic cancer through the cooperative efforts of the multiple disciplines of surgery, radiation, chemotherapy, pathology, immunology, and others. This involves planning, initiation, execution, analysis, and reporting of research methods related to management of patients with gynecologic malignancies as well as research dealing with any factors that may be related or influence the course of patients with gynecologic cancer.

Bowman Gray School of Medicine of Wake Forest University was approved for membership in the Gynecologic Oncology Group in June 1976. Cooperative action of investigators in Sections of Gynecologic Oncology, Hematology/Oncology, Radiation Therapy, and Surgical Pathology has promoted an interdisciplinary approach to the investigation of therapeutic regimens under study by the Gynecologic Oncology Group. The goal of accession of the maximum number of patient entries into Gynecologic Oncology Group protocols has been accomplished and is manifested by current participation in 28 groupwide protocols, with entry of twice as many patients as any other member in the Gynecologic Oncology Group during the past two years.

474. GYNECOLOGIC ONCOLOGY GROUP

Mikuta, J. J., Mangan, C. E., University of Pennsylvania, School of Medicine, Dept. of Obstetrics & Gynecology, *36th & Hamilton Walk, Philadelphia, Pennsylvania*, 19174, United States of America

Our institution is a member of the Gynecologic Oncology Group. The overall goals of the Group and the study protocols are described in the Group Chairman's grant application.

475. GYNECOLOGIC ONCOLOGY GROUP

Brady, L. W., Antoniades, J., Hahnemann Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *235 N. 15th St., Philadelphia, Pennsylvania*, 19102, United States of America

This institution is a participant in the Gynecologic Oncology Group. Overall goals of the Group and the Study Protocols are described in the Group Chairman's renewal application. Our institution will continue to register all new protocol cancer patients with the Group Operations Office and to participate in the Group Studies listed in a later section of this application. New protocols will be added as they become available. Moreover, our institution will coordinate and encourage the efforts of selected affiliated hospitals which are being enrolled in the program of national clinical cooperative trials.

476. FULL MEMBER INSTITUTION - GYNECOLOGIC ONCOLOGY GROUP

Hanjani, P., Vider, M., Smalley, R., Petersen, R., Temple University, School of Medicine, Dept. of Obstetrics & Gynecology, *3322 Broad St., Philadelphia, Pennsylvania*, 19122, United States of America

As a qualified and elected Full Member of the Gynecologic Oncology Group (GOG), the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Temple University Health Sciences Center, is seeking funding for accessing patients with gynecologic malignancies and pre-malignancies to Phase 2 and Phase 3 GOG clinical protocols and such Pilot Studies as may be deemed appropriate. The purpose of accessing patients is (1) to contribute toward the collaborative effort of attaining adequate sample sizes with standardized data so as to expeditiously compare the relative effectiveness of various regimens of surgery, radiation, chemotherapy, immunotherapy and combinations thereof in the treatment of gynecologic malignancies and (2) to promote and disseminate priority treatment methods to medical students, residents and community gynecologists. The treatment approach within Temple University Health Sciences Center will be multi-disciplinary and multimodality so that patients will have the maximum benefit of accumulated scientific knowledge for optimizing the prognosis of the disease.

Upon satisfaction of eligibility requirements on diagnostic factors and having given Informed Consent, patients will be centrally randomized (or assigned) treatment regimens as detailed in specific GOG protocols. Data on diagnosis, treatment, laboratory findings and required follow-up will be provided to the Group Headquarters and Statistical Office as prescribed by the specific protocol. Patients will be transferred to higher priority protocols when evidence of higher priority treatment is discovered by the collaborative effort of the Group.

477. GYNECOLOGIC ONCOLOGY GROUP HEADQUARTERS

Lewis, G. C., Thomas Jefferson University, Jefferson Medical College, Dept. of Obstetrics & Gynecology, *1025 Walnut St., Philadelphia, Pennsylvania*, 19107, United States of America

Using cooperative clinical trials, investigations of Phase II and Phase III type are being conducted in surgery, pathology, chemotherapy and radiation therapy, either alone or as combined modalities. This is being done in an effort to determine the most effective means for control of all varieties of gynecologic malignancies. Through Group efforts, coordinated by Headquarters and Statistical Office staffs, study protocols are constructed, activated and terminated. A specified data and Quality Control flow system assures production of meaningful observations. These are analyzed for best results. Methods found to be superior through clinical evaluations are then re-evaluated against other procedures, either new or standardly accepted in a continuum of evolution aimed at improving survival and progression-free interval.

478. GYNECOLOGIC ONCOLOGY GROUP

Mortel, R., Pennsylvania State University, Milton S. Hershey Medical Center, School of Medicine, Dept. of Obstetrics & Gynecology, *500 University Dr., Hershey, Pennsylvania,* 17033, United States of America

The overall objective of the Gynecologic Oncology Group is the improvement of treatment results in patients with gynecologic cancer by means of a multi-disciplinary approach. The Group is conducting clinical trials using accepted and new experimental treatments in a large number of patients with all types of gynecologic malignancy. Our institution will continue to register with the Gynecological Statistical Office all gynecologic cancer patients entering our hospital and will participate in all active and future protocols of the Gynecologic Oncology Group. We attend all semi-annual meetings of the group and actively participate via membership in several committees. We intend to become a primary resource for the Group's activity related to progesterone receptors in gynecologic cancer.

479. RADIATION THERAPY ONCOLOGY GROUP

Marks, R. D., Fitzgerald, R. H., Moore, T. N., Wallace, K. M., Adkins, W. Y., Medical University of South Carolina, School of Medicine, Dept. of Radiation Therapy, *80 Barre St., Charleston, South Carolina,* 29401, United States of America

Support is requested in this application for expanding the participation of the Division of Radiation Oncology of the Medical University of South Carolina in the activities of the Radiation Therapy Oncology Group. This department participates in radiation oncology programs at the Medical University of South Carolina and affiliated Roper Hospital in Charleston. The Division treats approximately 1200 patients a year, 1000 of these being new cancer patients. The Radiation Oncology Division has participated in the Radiation Therapy Oncology Group since 1973 and has been an active member since January 1974. Subsequent to the data above, approximately 200 cases have been accessioned into the various protocols of the Radiation Therapy Oncology Group. The Principal Investigator has been active in attending all meetings since 1974 and recently was appointed a member of the Site Visit Committee and a member of the Nominating Committee for the Group. The Principal Investigator has been an active participant in all working parties and has recently authored a Pilot Study involving hyperfractionation. To date the Division has entered a number of patients in the Lung Protocol, a split course protocol, mainly involving patients with carcinoma of the cervix, and the Head and Neck Protocol. At the present time we have submitted a contract proposal for the proposed study involving chemotherapy, radiotherapy, and surgery in treatment of advanced carcinoma of the head anc neck.

480. GYNECOLOGIC ONCOLOGY GROUP - INSTITUTIONAL GRANT

Buchsbaum, H. J., Forney, J. P., Graham, J. E., Hendler, F. J., Strauss, J. F., Frenkel, E. P., Graham, H. M., Blend, B. L., Jenevein, E. P., Fuller, D. E., Chan, R. C., Ronan, L., University of Texas, Health Science Center at Dallas, Southwestern Medical School, Dept. of Obstetrics & Gynecology, *5323 Harry Hines Blvd., Dallas, Texas,* 75230, United States of America

The University of Texas Health Science Center at Dallas is a full member of the Gynecologic Oncology Group (GOG). The Group's objectives and methods are described in detail in the Group Chairman's application.

The GOG is a national collaborative group whose objective is to improve the survival and quality of life of women with genital malignancies through a better understanding of the natural history of the diseases and the design of improved therapy. The Group is multidisciplinary, utilizing surgery, chemotherapy, radiation therapy and immunotherapy in clinical trials.

481. CANCER CONTROL PROGRAM FOR FAMILY PRACTITIONERS

Jackson, C. B., Maddox, P. F., Blumenschein, G. R., Nelson, R. S., Wharton, J. T., Martin, R. G., Jesse, R. H., University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Extramural Programs Division, *c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

The Cancer Control Program for Family Practitioners is designed to create an awareness of cancer as a disease and as a public health problem and to introduce the family practitioner to his role in cancer control at the community level. The program is offered in two parts: 1) an intrainstitutional rotation in oncology at UTSCC for family practice residents and 2) an extrainstitutional program in participating community hospitals. The one- or two-month rotation is divided into two-week segments devoted to four major sites of cancer: 1) breast, 2) head, neck, and skin, 3) gastrointestinal tract, and 4) gynecologic structures. The extrainstitutional program consists of educational programs in oncology given by UTSCC faculty at training hospitals for family practice residents that request them. Both components of the program provide current knowledge of prevention, detection, diagnosis, treatment, and rehabilitation of patients with cancer and of specialized facilities available and needed for these interventions.

482. GYNECOLOGIC ONCOLOGY GROUP (UTAH)

Johnson, G. H., Smith, W. G., Eyre, H. J., Eltringham, J. R., McDivitt, R. W., Utah Higher Education System, University of Utah, School of Medicine, Dept. of Obstetrics & Gynecology, *1400 E. 2nd S., Salt Lake City, Utah,* 84112, United States of America

The objective of the proposed research is to conduct collaborative clinical research in the treatment of gynecologic malignancies in cooperation with the other member institutions of the Gynecologic Oncology Group (GOG). The studies proposed include those protocols presently active and those to be approved as described in the Group Chairman's Grant Application, which also relates the overall goals of the GOG. These studies utilize a multimodal approach to the management of gynecologic cancer patients through input from gynecologic oncology, medical oncology, radiation therapy, pathology and immunology. This then affords the cancer patient with optimal care and service while evaluating and attempting to improve all phases of cancer management.

483. RADIATION THERAPY ONCOLOGY GROUP

Plenk, H. P., LDS Hospital, Radiation Center, *325 8th Ave., Salt Lake City, Utah,* 84103, United States of America

We will participate in various RTOG protocols to develop improved radiation therapy techniques in different types of cancer. We are proposing a new endometrial carcinoma protocol. We are developing instrumentation to improve heating by microwaves, and thermometry of hyperthermia and radiation will be combined in an attempt to improve the results of radiation therapy in advanced lesions. Specifically, we will do some basic development of equipment and of measurements with a 434-MHz applicator. We will test newly developed solid state probes to measure heat in depth within microwave fields.

INVESTIGATOR INDEX

Abeler, R.V. 176
Adam, E. 13, 100, 102
Adam, I. 94
Adam, S.A. 22
Adams, A.T. 119
Adamson, E. 238
Adeleye, J.A. 208
Adelusi, B. 88
Adkins, W.Y. 479
Ahlgren, M. 159
Ahmed, M. 139
Ahmed, Q.A. 137, 138
Aimakhu, V.E. 208
Aiman, E.J. 33
Aisner, J. 378, 412, 441
Al, I. 342
Albert, A.E. 336
Alert, J. 388
Alexander, E.R. 350
Alfaro Aceves, L. 264
Alford, C.A. 98
Aliferis, D. 24
Almeida, A.B. 438
Anderson, G. 197, 301
Anderson, G.C. 164
Anderson, M.C. 368
Anderson, T.W. 329
Anderson, W.B. 232
Anis, O. 465
Annegers, J.F. 44, 183
Antoniades, J. 475
Aoki, T. 430
Aoyama, M.H. 129
Arcangeli, O. 304
Armendariz, C. 385
Armentrout, S. 453
Armstrong, B.K. 17
Arnold, M.F. 25
Artzt, K. 224
Aruta, C.J. 392
Askari, S.A. 139
Asmussen, M. 389
Ataharuddin, Q. 136
Auersperg, N. 119
Auricchio, F. 49
Austin, J.M. 448
Austin, P. 453
Avedision, J. 304
Averette, H.E. 442
Axelrod, M. 467
Bacchetti, S. 111
Baggerman, L. 375
Baggs, R.B. 53
Bagshaw, M.A. 449
Bagshawe, K.D. 356
Bagwe, A. 348
Baisch, H. 340
Baker, L.H. 444, 463
Bakke, O. 72
Balavat, P.L. 348
Baldwin, R.W. 283, 358
Balint, R. 237
Ballou, B.T. 225
Baltzer, J. 189
Balzi, M. 298
Ban, J. 430
Banelli, E. 383
Baranovsky, A. 152
Barini, R. 330
Barker, E.A. 205, 303
Barnea, A. 33
Barnes, A.B. 13
Barone, R.M. 35
Barranco, S.C. 398
Barron, B.A. 334
Bartels, P.H. 345
Bartos, A. 160
Barzilai, D. 273
Bashir, H. 414
Bast, R.C. 415, 425
Beamer, W.G. 319
Bean, J.A. 170
Becciolini, A. 298
Becker, S.E. 278
BeckerBloemkolk, M.J. 110
Beebe, G.W. 164
Beecham, J.B. 469
Begent, R.H. 282
Beilby, J.S. 368
Bekesi, J.G. 405
Bekker, B.V. 322
Bellve, A.R. 260
Benenson, A.S. 150
Benitez Bribiesca, L. 264
Bennett, D. 223
Bensinger, W. 416
Bentivoglio, G. 382
Beral, V.S. 173, 174
Berger, E.G. 351
Berger, K. 89
Bernal, B.S. 299
Bernstein, S. 451
Bertoli, R. 148, 156, 427
Beth, E. 93
Bhamarapravati, N. 201
Bhardwaj, S. 405
Bhavnani, B.R. 40
Bibbo, M. 345, 367
Bicocca, C. 304
Bigatti, L.E. 330
Biggs, J.C. 414
Bighouse, K. 227
Birch, J.M. 175
Biso, T. 365
Bisson, G. 196
Biswal, N. 104
Biti, G. 298
Bjersing, L. 166
Bjoro, K. 38
Blair, O. 204, 302
Blend, B.L. 480
Blessing, J. 457
Blom , J. 456
Blom, P. 176
Blot, W.J. 164
Blumenschein, G.R. 69, 481
Bluthmann, H. 249, 250
Bocanera, R.A. 308
Boesen, E.A. 370
Boice, J.D. 164
Bolelli, G.F. 32
Bolognesi, L.T. 438
Boonyanit, S. 178, 187
Boots, L.R. 218, 277
Bordelon, M. 77
Boronow, R.C. 465
Bostad, L. 176
Boyes, D.A. 8
Bradbury, S. 295
Bradlow, H.L. 45
Brady, L. 457
Brady, L.W. 475
Braginski, J.E. 243
Brandes, J. 273
Branes, J. 146
Branton, P. 111
Breitenecker, G. 198
Bremond, A.G. 37
Brenelli, H.B. 330
Brenner, D.E. 378, 441
Brewer, J.I. 210, 211
Briggs, R.M. 23
Briner, W. 471
Briones, R.H. 439
Brody, J.A. 26
Brody, S. 42
Broggini, M. 424
Bronzert, D. 47
Brown, G. 104
Brown, J.B. 48
Bruckner, H. 405
Bryant, J.L. 317
Buchler, D.A. 78, 202
Buchsbaum, H.J. 480
Buckley, J.D. 85
Buckner, D. 416
Bullock, M.S. 473
Burki, K. 249
Bush, R.S. 386
Busutti, L. 384, 433
Buultjens, T.E. 246
Cabral, G.A. 107
Cadien, J.D. 261
Caldana, P.L. 382
Camacho, F. 467
Campbell, P. 467
Canaves, L. 308
Candiani, G.P. 284
Canellos, G.P. 437
Capelle, C. 239
Capua, A. 383
Caputo, T. 28, 181
Carasevici, E. 155
Cardoso, V.M. 361
Carl, P. 306
Carlstrom, K. 42
Carney, P. 453
Carr, B.I. 233
Carritt, B. 246
Carstensen, H.C. 422
Casanova, R.O. 147
Castaldo, T.W. 452
Castoria, G. 49
Cederloef, R. 193
Celoria, G. 304
Cerro, E. 304
Chabner, B. 47
Chabner, B.A. 403

Chahinian, A.P. 405
Chakrabarti, R.N. 134
Chan, R.C. 480
Charkviani, L. 185
Chen, J.S. 152
Chen, T.J. 54
Chen Wei, S. 257
Cheng, H.C. 54
Chernesky, M.A. 93
Chester, K.A. 252
Chiavetta, J. 99
Chilvers, C.E. 174
Chong, M.T. 47
Chorost, S. 181
Chou, J. 268
Chung, A.E. 243
Ciatto, S. 298
Cionini, L. 298
Clamon, G. 461
Clark, A. 90
Clark, J.H. 57
Clark Pearson, D. 470
Clarke, A.G. 283, 358
Clarke, E.A. 29, 40, 143, 329
Claudio, F. 93
Clemments, J.B. 103
Clingan, D.A. 309
Cohen, H.J. 471
Colabianchi, J.C. 304
Colas, A.E. 78
Coleman, C.N. 449
Colman, M. 453
Colombo, T. 424
Coltman, C.A. 410
Colton, T. 13
Colvin, M. 462
Connelly, R.R. 152
Connor, J.S. 73
Copeland, E.M. 69
Corrado, F. 384, 433
Corringham, R.E. 370
Cortes, P. 109, 281, 285
Cowan, K. 47
Cowdell, R.H. 295
Cramer, D.W. 180
Cramer, S.F. 182
Creasman, W.T. 391, 470
Croce, C.M. 250, 258
Crosignani, P.G. 428
Cummings, B.J. 386
Cummings, J. 376
Cupples, A. 336
Currie, J.L. 470
Curry, S.L. 446
Cutler, N. 46
Cuttner, J. 405
Czerwinski, W. 177
d'Ablaing, G. 213, 451
D'Incalci, M. 419, 423
Dabancens, A. 4, 21, 146, 162, 439
Damjanov, I. 262
Das Gupta, P.S. 134
Davies, J.I. 65
Davy, M.L. 426
Daw, E.G. 195
Day, N.E. 328
de Borges, R.J. 363
de Britton, R.C. 150
De Jong, G.A. 323
Decker, D.G. 27, 421
DeGiovanni, C. 59
DeLee, J.B. 14
Delgado, G. 455
Dembo, A.J. 386
Deobaghar, D.N. 108
DeSombre, E.R. 67, 267
deSrulijes, L.K. 273
Devare, S.G. 108
Devesa, S.S. 152
DeVita, V.T. 403
DeWolf, W.C. 260
Diaz, D. 388
Diaz Moragues, J. 331, 332
Dimitriades, M. 400
DiPillo, F. 467
DiSaia, P.J. 453
Djoseland, O. 38
Docherty, J.J. 106, 380
Doellgast, G.J. 257
Doll, R. 85
Doll, R.R. 3
Donelli, M.G. 424
Donner, A. 99
Donoghue, D.J. 254, 256
Doolittle, S. 24
Dreesman, G.R. 100
Dressman, G. 102
Driel, J.V. 375
Duboule, D. 241
Dunnick, N.R. 372, 373
Durand, R.E. 462
Dutta, H. 134
Duttagupta, C. 275
Dvivedi, M.S. 132
Easterday, C.L. 101
Ebihara, A. 130
Eckhardt, S. 199
Edman, C.D. 33
Efstratiadis, A. 255
Ehrlich, C.E. 460
Eigler, J. 189
Eikner, K.B. 72
Elahi, M.F. 136, 137, 138
Ellena, A. 156
Ellena, A.N. 148, 207, 427
Eltringham, J.R. 482
Elwood, J.M. 8
Endo, N. 209
Eppig, J.J. 259
Erba, E. 423
Escher, G. 467
Evain, D. 232
Evans, D.M. 326
Evans, R.W. 84
Evers, C.G. 465
Eyre, H.J. 482
Fabiyi, A. 88
Fairweather, D.V. 309
Faratian, B. 283
Fasano, E. 384, 433
Fay, J. 471
Fee, W. 449
Feit, C. 276
Fernbach, B. 405
Ferraz de Sampaio, L. 157
Fetter, B.F. 470
Filho, P.L. 361
Filler, R.S. 263
Fischer, D. 280
Fischer, D.B. 19
Fischer, J.J. 443
Fisher, R.I. 289, 403
Fishman, J. 45
Fishman, J.H. 45
Fitzgerald, R.H. 479
Flamigni, C. 32
Fleischman, R.A. 257
Fleites, G. 388
Fleming, H. 75
Floderus Myrhed, B. 193
Fodstad, O. 219
Fogh, J.E. 315
Fonseca, N.M. 293
Forney, J.P. 480
Fowler, W.C. 278, 472
Fox, C. 300
Fox, H. 368
Fragapane, S. 304
Franchimont, P. 71
Franke, H.R. 206
Franzosi, M.G. 419
Fraser, P.M. 174
Fraser, R.C. 196, 197, 301
Freedman, M. 336
Freeman, R.K. 453
Frenkel, E.P. 480
Freyre, R. 264
Friberg, L.T. 193
Friedl, H. 199
Friedman, S.J. 216
Frost, E.H. 112
Fu, Y.S. 274
Fuensalida, S. 21
Fukushima, D.K. 45
Fuller, D.E. 480
Fyfe, M.J. 471
Gaddis, O. 213, 450, 451
Gadomska, H. 177, 185
Gaitan Galarza, V. 127
Galesanu, M.R. 155
Gall, S.A. 470
Gallegos, G. 264
Galli, M.C. 59
Garcia de Alba, J.E. 158
Garcia Sainz, G. 385
Geil, R.G. 11
Geirsson, G.B. 328
Gentry, J. 151
Geraty, M. 467
Gerichter, C.B. 87
Gerschenson, L.E. 81
Geser, A. 93
Gharbi, R.M. 93
Ghersa, P. 424
Ghosh, A. 134
Ghosh, K. 134
Ghossein, N. 467
Giannopoulos, G. 65
Gilden, R.V. 108
Gingell, R. 12
Giordano, C. 147
Giordano, G. 93
Giraldo, G. 93
Girija, P. 396
Gitsch, E. 395
Glatstein, E. 403
Goelles, J. 125
Goes, J.C. 165
Gold, P. 46
Goldenberg, I.S. 19
Goldsmith, M. 405
Gomez, E. 388
Gonzales, M.R. 158
Gonzalez, O. 21
Goodall, H. 227
Goodwin, F.K. 46
Gopalan, N. 397
Gore, H. 448
Gorwill, R.H. 121
Gotoh, A. 131
Govan, A.D. 368
Gowing, N.F. 368
Grade, B. 239
Graham, F. 111
Graham, H.M. 480
Graham, J.E. 480
Graham, S. 24, 151
Grainger, J.L. 235
Gray, R. 5
Greco, V.F. 333
Green, G.H. 145
Greene, M.H. 164
Greenwald, E. 467
Greenwald, E.S. 406

Greenwald, P. 24, 28, 151, 181
Grelich, F. 200
Griffiths, C.T. 180
Grilli, S. 59
Gronoos, M. 36
Grontoft, O. 310
Guman, N. 366
Gurpide, E. 75, 76
Gusberg, S.B. 75
Gusdon, J.P. 473
Gvamichava, D. 185
Habbema, J.D. 323
Habib, Z. 296
Hahnel, R. 17, 61, 62, 63
Haije, W.G. 375
Hakala, T.R. 225
Hakama, M.K. 161
Hamamoto, T. 130
Hammond, C.B. 214, 470
Hampar, B. 108
Hanjani, P. 476
Hanker, J. 471
Hankey, B.F. 152
Haque, M.N. 136, 138
Hardin, J.W. 57
Haring, M. 31
Harris, R.W. 85
Hart, H. 115
Hart, R. 405
Harwood, A.R. 386
Hashimoto, T. 131
Haskill, J.S. 278
Hatch, K.D. 447, 448
Haugen, H.N. 38
Haughom, J.R. 215
Hebel, J.R. 97
Hecht, F. 261
Heggie, A.D. 182
Heise, H.W. 152
Heller, P. 456
Hendler, F.J. 480
Hendrick, J.C. 71
Heneen, W.K. 296
Henschke, U. 192
Herbst, A.L. 14, 52, 70, 367
Herity, B.A. 141
Hernandez, W. 451
Herzig, G.P. 413
Herzog, R.E. 379
Hickey, R.C. 69
Hickman, B.T. 465
Hill, B.T. 429
Hill, C.S. 69
Hill, E.C. 92
Hill, L.T. 455
Hill, M.J. 376
Hill, R.P. 386
Hill, S. 368
Hilton, J. 462
Himori, T. 405
Hiza, P.R. 192
Hoff, M. 24
Hogan, B. 220
Hoglo, S. 38
Holford, T.R. 19
Holland, J.F. 405
Holt, J.A. 68
Homem de Melo, M.R. 147
Homesley, H.D. 473
Hoskins, W.J. 456
Hossain, M.A. 136, 137, 138
Houts, P.S. 446
Houx, H. 206
Huang, A.T. 471
Huraux, J.M. 93
Hustin, J. 71
Hutchison, G.B. 180
Ibrahim, A.N. 349
Iglesias, J. 297
Iglesias, J.M. 390
Ikeda, H. 343
Ikegawa, S. 45
Illmensee, K. 241, 249, 250
Illmensee, R. 241
IngelmanSundberg, A. 42
Isarangkul Na Ayuthya, W. 6, 201
Islam, K.M. 136, 137, 138
Iversen, D.E. 58
Iwakawa Shiga, L. 116
Jackson, C.B. 481
Jacobs, C. 449
Jacobs, H. 41
Jafarey, N.A. 139
Jaffe, E. 289
Jain, D.C. 163
Jain, M. 9, 144
Jain, S.P. 163
James, V.H. 41
Janerich, D.T. 24
Janis, M. 467
Janne, O. 60
Jasonni, V.M. 32
Jenevein, E.P. 480
Jensen, E.V. 80
Jensen, P. 280
Jesdinsky, H.J. 10
Jesse, R.H. 69, 481
Jick, H. 171
Jimenez Medina, J. 388
Jobson, V.W. 473
Johannesson, G. 328
Johansson, E. 18
Johnson, D.C. 54
Johnson, E.F. 122
Johnson, G.H. 482
Johnson, L. 101, 414
Johnson, M.H. 227
Johnsson, J.E. 159
Johnston, G.A. 14
Johnston, J.M. 33
Joines, W. 471
Jones, J.M. 326
Jones, P.K. 182
Joplin, C. 150
Joslin, C.A. 324
Judd, H.L. 34, 35
Juillard, G.J. 417
Junaid, T.A. 191, 208
Kabir, A. 136, 137, 138, 188
Kagawa, Y. 130
Kahan, B.W. 221
Kaiser McCaw, B. 261
Kammerman, S. 55
Kaplan, B.H. 467
Kappas, A. 45
Karacsony, I. 160
Karin, M. 257
Karrer, K. 199
Kashida, R. 343
Kater, L. 347
Kato, T. 209
Kaufman, D.G. 74
Kaufman, R.H. 13, 94, 100
Kauppila, A. 60, 357
Kawaguchi, T. 131
Keen, J. 359
Keen, P. 149
Kellen, J.A. 360
Kelley, R. 239
Kelloff, G.J. 108
Kelsey, J.L. 19
Kempson, R. 449
Kenemans, P. 206
Kessler, I.I. 89, 97
Ketting, B.W. 110
Keusch, G. 405
Kewitz, H.P. 10
Khair, M.A. 136, 138
Khaleque, S.A. 136, 137, 138, 188
Khaliq, A. 411
Khan, A.S. 108
Khoury, G. 244
Khurana, B.B. 292
King, E.B. 92
Kirk, D.J. 309
Kirk, R.L. 348
Kitao, M. 321
Kjellgren, O.R. 166
Kleinerman, R. 164
Klemi, P.J. 36, 307
Kligerman, M.M. 387
Knapp, R. 65
Knapp, R.C. 415, 418
Knapp, W. 395
Kochar, M. 292
Kocsis, S. 199
Kodama, M. 129
Kodama, T. 129
Koffler, D. 73
Kohler, P.O. 77
Kolstad, P. 389
Konits, P. 412, 441
Koper, C.J. 342
Kopin, I.J. 46
Koren, H.S. 280
Koss, L.G. 339
Kotwani, B.G. 292
Krakoff, I.H. 399
Krishnamurthi, S. 396, 397
Kudo, J. 209
Kuehn, D.J. 251
Kulcar, Z. 89
Kummerlaender, L. 86
Kurland, I. 13
Kurman, R. 455
Kwalick, D.S. 338
Kyalwazi, S.K. 93
La Storia, S. 49
Lacroix, A. 47
LaGasse, L.D. 35, 393, 409, 440, 452
Lagrelius, A. 42
Lahousen, M. 125
Lamvik, J. 72
Land, C.E. 164
Landsman, J.B. 326
Langley, F.A. 368
Lantta, M. 64
Laszlo, J. 471
Lau, H.U. 185
Lauritzen, C. 20
Lawrence, C.E. 24, 28
Leavitt, W.W. 66, 84
Lee, H. 79
Lee, R. 456
Lehman, J.M. 252
Leivo, I. 228
Leman, M. 456
LePage, G.A. 411
Leventon Kriss, S. 87
Levine, A.J. 230, 237, 240, 251
Levine, D. 93
Levy, C.C. 104
Levy, D.S. 447
Lewis, G.C. 457, 477
Lewis, J.L. 39, 45, 117, 212, 354
Lewis, M. 243
Lewy, A. 46
Leyte, L. 342
Liberati, A. 419
Lickrish, G. 143, 154
Lifshitz, S. 170, 461
Lin, C. 371
Lin, R.S. 97
Lindberg, B. 18

Lindberg, L.G. 159
Linden, W.A. 340
Lindsay, J. 153
Linney, E.A. 253
Linsenmayer, T. 222
Lippman, M. 403
Lippman, M.E. 47
Little, C.D. 222
LiVolsi, V.A. 19
Lloyd, K.O. 286, 354, 374
Lo, A. 230
Lo, C.W. 255
Lonser, A. 383
LoBue, C. 23
Lodi, S. 32
Longo, D. 403
Lovric, B. 402
Luande, J. 192
Lucas, W.E. 43
Luini, W. 284
Lunde, O. 38
Lundman, T. 193
Lunell, N.O. 42
Luthra, U.K. 292
Ma, D. 414
Mabuchi, K. 97
MacDonald, C.M. 246
MacDonald, J. 455
MacDonald, P.C. 33
MacGregor, J.E. 142
Machado, J.C. 165
Macnab, J.C. 103
MacQueen, H. 245
Maddon, D.L. 101
Maddox, P.F. 481
Madhav, R. 243
Magrini, S. 298
Major, F.J. 454
Malamud, L. 304
Malkin, A. 360
Mancini, M. 419
Manell, P. 18
Mangan, C.E. 474
Mangioni, C. 279, 436
Mann, D. 289
Mano, T. 268
Mantovani, A. 279, 284, 419
MarcianoCabral, F. 107
Markey, S. 46
Marks, R.D. 479
Marsden, H.B. 175
Marshall, J. 151
Marshall, R.B. 473
Martin, G.R. 234, 256
Martin, J.D. 62
Martin, P.M. 149
Martin, R.G. 481
Martinez, A. 449
Martinez, L. 4
Martinez Hernandez, A. 262
Martucci, C. 45
Marun, M. 304
Masi, C.A. 148, 156, 207, 427
Mason, T.J. 164
Masood, S.M. 139
Masubuchi, K. 167
Mattison, D.R. 122
Maurizi Enrici, E. 383
May, E. 244
MayliePfenninger, M.F. 223
McBurney, M.W. 226, 229, 247
McCormack, S.A. 217
McDivitt, R.W. 482
McGowan, L. 179
McIlhinney, G. 227
McPherson, K. 3
Meade, T.W. 376
Meerwaldt, J.H. 375
Meisels, A. 114
Melnick, J.L. 100, 102
Menczer, J. 87, 118, 184
Mendelsohn, I. 164
Mendelson, W. 46
Mendoza, M. 264
Mettlin, C. 151
Metzgar, R.S. 471
Mgaya, M. 192
Miah, M.N. 137, 138, 188
Mickey, M.Y. 91
Migliaccio, A. 49
Mikaelian, S. 37
Mike, V. 93
Mikuta, J.J. 478
Miller, A.B. 9, 144, 153
Miller, R.K. 53
Miller, R.W. 446
Mintz, B. 257
Mirand, E. 151
Mladineo, J. 465
Modan, B. 5, 184
Modan, M. 87, 118
Mohapatra, L.N. 292
Moldow, C.F. 108
Molina, R. 4
Monaco, M.E. 47
Moore, T.N. 479
Moragues, J.D. 330
Morasca, L. 423
Morgan, R.W. 16, 154
Moriarty, M. 141
Morris, J.M. 19
Morrow, C.P. 213, 450, 451
Mortel, R. 82, 478
Mortimer, E.A. 182
Mostow, E. 19
Muindi, J.N. 192
Mundt, D.J. 164
Mungai, V. 298
Munteanu, S. 128
Murphy, J. 141
Murphy, P. 24
Musacchio, R.M. 148, 156, 207
Muss, H.B. 473
Muto, M.G. 84
Muzaferija, A. 402
Myers, C. 403
Myers, M.H. 152
Nagai, M. 168
Nagarajan, B. 396
Nagarajan, L. 232
Nahmias, A. 96
Naib, Z.M. 96
Nalewaik, R.P. 108
Nalick, R.H. 213, 450, 451
Narayanan, M. 133
Narvaez, C.R. 291
Nasca, P.C. 181
Navarini, H. 304
Naves, A.E. 365
Neglia, W. 456
Neill, W. 115
Nelson, R.S. 481
Nemoto, H. 167
Neuser, D. 327
Newsome, D. 46
Ngu, V. 93
Niell, H.B. 406, 407
Nikolaeva, D.V. 172
Nishizuka, Y. 50
Nogueira de Carvalho, C.R. 147
Norris, H.J. 270, 311, 312, 314
Norris, J.S. 77
Norton, B. 45
Norval, M. 115
Norvell, M.J. 51
Noss, T. 321
Nye, E.B. 145
O'Brien, T.J. 213, 450, 451
O'Conner, J.F. 45
Obradovic, M. 124
Oda, S. 131
Ojeda, J.M. 109, 281, 285
Okagaki, T. 344
Okama, M.N. 147
Old, L.J. 288, 354
Oliveira, A.M. 361
Oliveira, V.F. 157
Olsnes, S. 219
Onsrud, M. 290
Onuigbo, W.I. 190
Oppenheimer, S.B. 239
Order, S.E. 462
Ory, H.W. 7
Osborn, R.W. 29
Osobe, D. 401
Ostergard, D.R. 453
Ostrow, S. 412
Osunkoya, B.O. 88
Oud, P. 341
Ozols, R. 403
Pacini, P. 298
Pacsa, A.S. 86
Pala, F.L. 2
Paleoch, Y.Y. 26
Pandey, U.C. 163
Paredes, A. 297
Park, R.C. 456
Parker, C.R. 33
Parker, R.T. 470
Parkin, D.M. 324
Pass, R. 98
Pastene, L.L. 330
Pasternak, S. 162
Pateman, J.A. 246
Pati, B.P. 138
Patra, G.H. 134
Pavic, A. 402
Pazzaglia, G. 384, 433
Peakman, D.C. 261
Pearson, L. 239
Pejtsik, B. 86
Penny, R. 414
Pepperell, R.J. 48
Periti, P. 436
Persaud, V. 126
Persson, I.R. 18
Pescetto, G. 382
Peter, Z. 199
Petersen, R. 476
Peterson, R. 337
Petounis, A. 400
Petrilli, E.S. 452
Petty, W.M. 431
Petzoldt, U. 241, 249
Phillip, J. 192
Pickel, H. 125
Pierce, G.B. 252
Pilch, Y.H. 35
Pilot, A. 382
Pinheiro, L.R. 165
Pinotti, J.A. 330, 331, 332
Plant, M. 295
Platz, C. 461
Plenk, H.P. 483
Plesko, I. 199
Ploem, J.J. 342
Ploem, J.S. 342
Plough, A. 336
Polentarutti, N. 284
Pompe Kirn, V. 199
Ponciano, B.R. 293
Pontes Cunha, M. 294
Ponticelli, P. 298
Pookim, Y.L. 359

Porter, J.C. 33
Potter, W. 46
Poulakou, E. 400
Prado, R. 146
Prem, K.A. 464
Price, L.A. 429
Prince, E. 23
Prior, M.P. 194
Prorok, P.C. 152
Pukkala, E. 161
Pun, A. 414
Punnonen, R. 36
Quattropani, S.L. 320
Quinn, M. 48
Raaymakers, M. 341
Rabes, H.M. 306
Radzuweit, H. 1
Ragni, N. 382
Rahim, M.A. 136, 137, 138, 188
Rainer, H. 395
Rao, B.R. 123
Rao, Y. 453
Ratajczak, T. 61, 62, 63
Rattenhuber, U. 306
Rauramo, L. 36
Rauth, A.M. 386
Ravnihar, B. 199
Rawls, W. 99
Rawls, W.E. 90, 111
Raymond, L. 124
Razis, D.V. 400
Reagan, J.W. 274
Reale, F.R. 367
Ree, E. 110
Reed, M. 41
Reeves, G. 304, 305
Reeves, W.C. 150
Rehamm, G. 139
Reich, N. 230
Reisner, E. 471
Reuter, L.A. 84
Reynolds, D.W. 98
Reynolds, F.H. 108
Ribbons, L. 239
Rice, R.H. 317, 318
Rich, W.M. 453
Richardson, G.S. 265, 377
Richart, R. 28, 181
Ricketson, G. 465
Rider, W.D. 386
Rieper, J.P. 293
Rimondi, C. 384, 433
Risberg, B. 310
Ritz, J. 415
Robboy, S.J. 13, 14
Robinson, S.C. 196, 197, 301
Rochet, Y. 37
Rodriguez, C. 385
Ron, E. 5
Ronan, L. 480
Roncoroni, E. 308
Rose, L.I. 73
Rosenberg, S. 403
Rosenberg, S.A. 449
Rosenborg, L. 42
Rosenfeld, R.S. 45
Rosenshein, N. 462
Rosenstraus, M.J. 231, 236
Rotman, M. 468
Rotondi, A. 49
Roy, N.N. 134
Roy Chowdhury, J. 134
Rubin, P. 434, 435
Russell, L.B. 263
Rutishauser, I. 376
Rutledge, F.N. 69
Rydnert, J. 166
Sachs, H. 200
Sacks, T.L. 108
Sadler, E. 366
Saha, I. 134
Saito, K. 321
Salas, C.O. 4, 146, 297, 390
Salsano, F. 383
Samaan, N.A. 69
Sampaio Goes, J.E. 157
Samuel, K.C. 163
Sanani, S. 408
Sanford, J. 84
Sarda, I.R. 121
Sarkhel, T. 134
Sarma, S.K. 138, 188
Sarnoff, P. 237
Sarnow, P. 230
Saunders, V. 194
Sawada, E.A. 335
Saxton, W. 239
Scarpati, D. 382
Schachter, J. 92
Schaffer, P.A. 105
Schiavone, E. 49
Schlaen, I. 308, 362, 365
Schlaerth, J.B. 213, 450, 451
Schlegel, S. 268
Scholz, K. 340
Schuette, B. 269
Schulman, N. 333
Schulz Contreras, M. 127
Schwartz, C. 238
Schwartz, M. 336
Schwartz, N.B. 56
Schwartz, P.E. 19
Schwarzbein, A. 239
Scotto, J. 164
Scully, R.E. 14, 180
Sebastien, P. 6
Segadal, E. 58, 176
Segal, S. 244
Seidl, A. 198
Seigler, H.F. 471
Sekikawa, K. 237
Sekine, S. 186
Sekiya, S. 209
Sessa, C. 423
Seth, P. 292
Sha, S.P. 134
Shaba, J. 192
Shah, C.A. 135
Shanta, V. 396, 397
Shaper, J.H. 353
Shapiro, S. 30, 169
Sharp, F. 103
Shawker, T. 372
Sheid, B. 271
Shen, J. 213, 451
Sherman, B.M. 170
Sherman, M.R. 83
Shigematsu, T. 321
Shingleton, H.M. 447, 448
Sibary, K. 140
Siddiqi, M. 139
Sierra, D. 305
Sikdar, S. 134
Sikic, B. 449
Silveira, G.G. 438
Silveira, J.G. 438
Silverberg, S.G. 313
Silverman, D.T. 152
Simon, R. 403
Singh, K.N. 163
Sirajoddowla, M. 137, 188
Skehan, P.J. 216
Slankard Chahinian, M.L. 405
Slone, D. 30
Sly, L.D. 113
Smalley, R. 476
Smedby, B. 18
Smiley, J. 111
Smith, C.L. 122
Smith, J.P. 69
Smith, M.L. 466
Smith, P.G. 173
Smith, W.G. 482
Solter, D. 242
Sonnenschein, C. 79
Sorensen, S. 239
Soto, A.M. 79
Spaulding, M.B. 408
Spengler, R.F. 29
Spreafico, F. 279
Spriggs, A.I. 295
Srisupandit, S. 6
Stafl, A. 364
Stalsberg, H. 176
Standfast, S.J. 24
Stanek, E.J. 152
Stavraky, K.M. 99
Stocchi, Y. 384, 433
Steele, H.D. 121
Steiner, J.W. 458
Steinhorn, S.C. 152
Stematsky, G.T. 118
Stenman, U. 64, 266
Stephenson, J.R. 108
Stern, E. 91
Stewart, P. 416
Stewart, T.A. 257
Stoa, K.F. 58
Stockdale, F. 449
Stolbach, L.L. 355, 371
Stolk, J.G. 206
Stone, B.J. 164
Stowe, S. 451
Strauss, J.F. 480
Streefkerk, M. 347
Suarez, M. 109, 281, 285
Subak Sharpe, J.H. 246
Suttle, D.P. 430
Swartzendruber, D.E. 248
Sweetnam, P.M. 326
Swindell, R. 175
Sychra, J. 345
Symonds, E.M. 283, 358
Syrjala, P. 60
Szamborski, J.J. 177
Tada, M. 321
Taft, P.D. 14
Tai, D. 465
Taina, E.J. 432
Takagi, N. 256
Takamizawa, H. 209
Takasugi, M. 91
Talerman, A. 375
Tamarkin, L. 46, 47
Tanaka, N. 343
Tanaka, S. 31
Tanke, H.J. 342
Tate, J. 245
Tatra, G. 395
Tavassoli, T. 312
Taylor, J. 345
Taylor, P.T. 447, 448
Taylor, R.W. 309
Teitelbaum, C. 333
Teixeira Fernandes, R. 203
Teper, S. 142
Terasaki, P. 91
Terra, P.I. 361
Tetreault, J. 84
Tewfik, H. 461
Thigpen, J.T. 465
Thomas, D.B. 5
Thomas, E.D. 416, 420
Thomas, G.M. 386

Thompson, D.W. 9, 144
Thorgeirsson, S.S. 122
Thorsby, E. 290
Tichy Racs, M. 199
Todd, P.W. 106, 380
Tognoni, G. 419
Toledo, P. 297
Toledo, P.H. 390
Tombolini, V. 383
Torain, B. 269
Torres, A.F. 2
Tosello, J.R. 165
Totani, R. 129
Townsend, D. 13
Townsend, D.E. 15, 213
Tsukamoto, T. 45
Tucker, D.F. 359
Tucker, R.S. 333
Tulinius, H. 328
Tuskan, E. 402
Tveit, K.M. 219
Twaddle, E. 61
Tyrey, L. 214
Ucci, A.A. 79
Ueno, T. 343
Ullrich, R.L. 120
Ultmann, J.E. 70
Undevia, J.V. 348
Urbach, G.I. 352
Utaaker, E. 58
Vaheri, A. 228
Vakil, D.V. 16
Valenti, J.L. 304
van de Linde, A.W. 347
van de Ven, W.J. 108
Van de Walle, R.T. 341
van den Berg, F.M. 110
Van der Maas, P.J. 323
Van Haelen, C. 289
Van Oortmarssen, G.J. 323
vanDriel, A.J. 342
Vanhatalo, J.H. 432
vanIngen, E.M. 342
Vardthanausera, C. 187
Vasey, D. 358
Vatter, A.E. 216
Vazquez Curiel, A. 385
Veling, S. 322
Verdon, B. 351
Verwoerd, N.P. 342
Vessey, M.P. 3, 22, 85
Vestergaard, B.F. 95
Vider, M. 476
Vihko, R. 60
Villa, H. 308
Villafane, S.E. 261
Villagran, L.J. 299
Vincent, P. 414
Virtanen, I. 228
Vistica, D.T. 269
Vitturini, A. 383
Vogl, S.E. 394, 467
Vollovitch, Y. 184
Volk, H. 467
Von Hoff, D.D. 369
Vooijs, P.G. 206, 322
Vooys, G.P. 341
Vrolijk, J. 342
Wacker Pujdac, B. 177
Wagner, E. 257
Wagner, G. 395
Waien, S. 239
Wakefield, J. 140
Walboomers, J.M. 110
Walker, L.C. 359
Walker, W.P. 455
Wall, C. 153
Wallace, D. 450
Wallace, D.L. 213
Wallace, K.M. 479
Wallace, R.B. 170
Walton, L.A. 278, 472
Ward, D.N. 69
Wartiovaara, J. 228
Watanabe, S. 343
Waterhouse, J.A. 194
Waxster, F.X. 11
Weber, G. 430
Wood, J.C. 470
Wehr, T. 46
Weisbaum, G. 456
Weisman, A.D. 445
Welander, C.W. 354
Welch, W.R. 180
Weller, S.K. 105
Westerholm, B. 18
Westgaard, G. 176
Whang Peng, J. 403
Wharton, J.T. 481
White, A. 26
White, C. 19
Whitmore, G.F. 386
Whitmore, W. 272, 381
Wied, G.L. 345, 346
Wielenga, G. 342
Wiernik, G. 295
Wiernik, P.H. 378, 412, 441
Wilbanks, G.D. 459
Wilkie, N.M. 103
Williams, A.O. 191
Williams, P.T. 85
Wilson, J.D. 33
Wiser, W.L. 465
Wolf, A. 20
Woodcock, A.S. 368
Woodward, K.T. 470
Woolever, C.A. 29, 40
Worden, J.W. 445
Wrba, H. 199
Wright, L.H. 145
Wunderlich, J.R. 289
Yamaguchi, S. 167
Yanagawa, H. 131
Yang, K.P. 69
Yokoyama, H. 131
Yordan, E. 450
Yordan, E.L. 213
Young, R.C. 289, 403
Young, R.H. 14
Younger, J.B. 448
Yuasa, S. 186
Yule, R. 325
Yunis, E.J. 260
Zaebst, D. 31
Zahniser, D. 341
Zaidi, M.H. 139
Zanartu, J. 21
Zangerle, P.F. 71
Zubrod, C.G. 316
Zyngier, S.B. 165

CURRENT CANCER RESEARCH PROJECT REGISTRATION FORM

Send to: **ICRDB PROGRAM**
National Cancer Institute
5333 Westbard Avenue
Westwood Building, Room 10A18
Bethesda, Maryland 20205

ICRDB NUMBER

DO NOT WRITE HERE

PLEASE READ SPECIAL INSTRUCTIONS ON OTHER SIDE

If you have already submitted a description of your research to the Smithsonian Science Information Exchange (SSIE), to the Clearinghouse for Ongoing Research in Cancer Epidemiology in Lyon, France, or to the Current Cancer Research Project Analysis Center (CCRESPAC) within the past eight (8) months, please do not fill out this form.

PLEASE TYPE OR PRINT IN ENGLISH

1) FULL TITLE OF CURRENT CANCER RESEARCH PROJECT

2a) UNIQUE PROJECT IDENTIFICATION NUMBER(S)

2b) PROTOCOL NUMBER(S) (if applicable)

3) NAME OF ORGANIZATION WHERE RESEARCH IS PERFORMED

DEPT./LAB./UNIT:

MAILING ADDRESS (see item F on reverse side):

COUNTRY:

4) INVESTIGATORS (use 2 initials & last name)

PRINCIPAL:

CO-INVESTIGATORS:

5) NAME OF FUNDING ORGANIZATION(S) (list principal source first)

6) GIVE MONTH AND YEAR FOR END OF CURRENT FUNDING

7) DESCRIBE PROJECT UNDER THREE HEADINGS: 1) OBJECTIVE; 2) APPROACH; AND 3) PROGRESS (optional) (use specific, technical terms)

PLEASE CHECK ONE: ______ 1. This is a description of a NEW Project.
______ 2. This is a REVISED description of Project No. ______________
(Insert identification number)

FORM APPROVED: OMB NO. 068-R1441 EXP. AUG. 1983

CANCER RESEARCH REGISTRY

A Service of the National Cancer Institute

INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM

You are invited to complete a Current Cancer Research Project Registration Form PROVIDED you have NOT completed a similar form for the Smithsonian Science Information Exchange (SSIE), the Clearinghouse for Ongoing Research in Cancer Epidemiology in Lyon, France, or for the Current Cancer Research Project Analysis Center (CCRESPAC) during the last eight months.

Your project description will be entered into the National Cancer Institute's (NCI) data base, CANCERPROJ (**Cancer Projects**). Your project description will also appear in one or more of the ICRDB publications known as SPECIAL LISTINGs of Current Cancer Research. Every year the ICRDB publishes fifty SPECIAL LISTINGs, each containing project descriptions in different specific oncology research areas. A free copy of a SPECIAL LISTING is automatically sent to each investigator whose project description appears in that SPECIAL LISTING. Thus, investigators are annually made aware of research being carried out in their areas of interest.

GUIDELINES FOR FILLING OUT THE REGISTRY FORM

A. The description should be submitted by or through the individual who is the **principal investigator** of the project described. Major co-investigators should also be listed.

B. If you are working on more than one project, or if your one project consists of several distinct major segments, please prepare a separate summary form for each.

C. Only **CANCER** research projects which are CURRENTLY **ACTIVE** and CURRENTLY **FUNDED** should be submitted.

D. If you are submitting a clinical protocol, please send a copy of the complete protocol. The NCI has an established format which will be used to develop a standard protocol summary. A copy of the prepared summary will be sent to you for review prior to its entry into the data base.

E. Return to address shown on the front of this form.

F. IMPORTANT. If you prefer to have your copy of the SPECIAL LISTING mailed to your home address, or if your co-investigators have different mailing addresses, please list each name and address on a separate sheet of paper.

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS

Penalty for Private Use, $300

PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

SL-422

NOTICE OF MAILING CHANGE

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616